UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE COMPANY, JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY and MANULIFE INSURANCE COMPANY, Plaintiffs, v. ABBOTT LABORATORIES, Defendant.	CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF JEANNE M. FOX

I, Jeanne M. Fox, do hereby declare and say:

1. My name is Jeanne M. Fox. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

Education and Employment Background

2. I am currently employed by Abbott Laboratories ("Abbott") as Divisional Vice President of the North American Regulatory Affairs department in Global Pharmaceutical Regulatory Affairs. I was appointed to this position in October 2007. I currently report to Dr. David Wheadon, Group Vice President, Global Pharmaceutical Regulatory Affairs.

3. In 1975, I received a Bachelor of Science degree in Chemistry from MacMurray College. I received a Master of Science degree in Medicinal Chemistry from the Purdue University Graduate School of Pharmacy in 1978.

4. In my position as Divisional Vice President of North American Regulatory Affairs, I am responsible for managing the Regulatory Affairs group that works to obtain U.S. regulatory approval for products to be marketed in the United States and for supporting the Regulatory Affairs staff at the Abbott Canada affiliate in their interactions with Health Canada. We are responsible for review and submission of applications for approval by the United States Food and Drug Administration (FDA), as well as for making routine submissions to the FDA.

5. I have been employed by Abbott for approximately 18 years. During that time I have worked on regulatory issues in connection with more than 20 compounds in development. I have represented Abbott before the FDA in connection with all those compounds. From approximately 1993 until approximately November 2002, I was a Director of Regulatory Affairs in Abbott's Pharmaceutical Products Division (PPD). My responsibilities in that position varied over time. During the period 1993 until 2001, I was responsible for regulatory issues related to the anti-infectives and anti-virals therapeutic areas, including having products in these therapeutic areas submitted to and approved by regulatory agencies in the United States. In order to fulfill my responsibilities in this regard, I was also responsible for being aware of regulatory requirements, including FDA requirements, and for conveying information about these requirements to the project teams I worked with, including the ABT-773 project team. At approximately mid-year 2001, I transitioned out of anti-infectives and anti-virals to

immunoscience and metabolism, with similar responsibilities. In November 2002, I became a Senior Director in the Regulatory Affairs group within PPD, with similar responsibilities for the immunoscience and metabolism therapeutic areas as I had as Director. As a result of restructuring to create a global regulatory affairs function, in January 2004 I was appointed to manage the US Regulatory Affairs Department within Global Pharmaceutical Regulatory Affairs.

Responsibility for ABT-773

6. I began working on ABT-773 when I was a Director of Regulatory Affairs. I worked on the regulatory aspects of this anti-infective compound from the time it was first brought into development by Abbott until I transitioned to immunoscience and metabolism in approximately mid-2001. It is my understanding that at the time I transitioned to immunoscience and metabolism in mid-2001 ABT-773 was still under development by Abbott.

Responsibility for Working with the FDA Regarding ABT-773

7. During the period I worked on ABT-773, I was the regulatory person responsible for making sure that the appropriate filings for ABT-773 were made with the FDA and for helping the ABT-773 team to move the product forward to gain regulatory approval, either directly, or by supervising my staff member, Greg Bosco, who worked on ABT-773.

8. During the period I worked on ABT-773, I attended meetings with the FDA about the compound in person and by telephone. During those meetings, I was generally the senior Regulatory Affairs person present. One of my responsibilities was to identify and understand any issues raised by the FDA regarding the development of ABT-773, to

communicate any such information about ABT-773 to the project team, and to help resolve any such issues.

The FDA and QT Prolongation and Liver Toxicity Issues

9. Based on my experience within the pharmaceutical industry and with the FDA during the late 1990s and early 2000s, I understood in 2000 and 2001, while I was working on the ABT-773 project, that the FDA considered the potential for QT prolongation, which I understand to be a delay in one of the electrical signals in the normal action of the heart, to be a prominent issue for all drugs, including anti-infectives, that needed to be addressed in preclinical and clinical trials. This general FDA concern regarding a drug's potential for QT prolongation, as discussed at meetings with the FDA that I attended during this period, is reflected, for example, in a set of draft slides that I prepared in late November 2000 for presentation to Abbott's senior management, setting forth my understanding regarding the ABT-773 End of Phase II meeting with the FDA that occurred on November 27, 2000, and which is discussed below. Attached hereto as D's Exhibit 780 is a true and correct copy of the email dated November 29, 2000 that I prepared and sent to various Abbott employees attaching the "first draft" of these slides. In a draft slide titled "ABT-773 regulatory issues," I note, among other things, that the "QT issue is hot button for FDA". D's Exhibit 780 at ABBT0556818. By that phrase, I meant an issue that seemed to me to be a prominent or important topical issue for the FDA at the time that Abbott needed to be aware of and address. QT prolongation was at this time a fairly new issue for the FDA. As such, the FDA had to assess how it should be studied, the best method of testing for it, and what kind of direction the FDA was

going to give to drug sponsors and ultimately what kind of assessment would lead to what kind of labeling for any particular compound.

10. Consistent with this general focus on a new, topical issue, it is my recollection that the FDA requested that we characterize the QT prolongation potential for ABT-773. Since the FDA had not completely defined how a drug sponsor such as Abbott would document how a particular class of drugs or a particular compound had no significant QT prolongation, it was unclear what testing method and what safety database would be sufficient to show that a compound did not have the potential to prolong QT. It was my understanding, based on my participation in discussions with the FDA, that the FDA's concern about the potential for QT prolongation was not based on any data regarding or otherwise specific to ABT-773.

11. Similarly, I recall that during this same period the FDA had a general concern with the potential for hepatotoxicity of all pharmaceutical compounds, including anti-infectives. In February 2001, I attended an FDA meeting for the industry in Washington, D.C., in which information was presented by the FDA and academics on what was known about hepatotoxicity caused by drugs and how scientists could develop screening tests and data to enable drug sponsors to predict more accurately which compounds in development might have hepatotoxicity issues. Among other things, the FDA was encouraging more sharing of data from products that had been pulled from the market for liver toxicity issues. Since this conference occurred shortly after one of the major quinolones was withdrawn from the market as a result of hepatotoxicity issues, the question of the potential relationship between liver toxicity and anti-infectives in general was also discussed at this industry-wide meeting. There was general discussion at the

conference regarding what might be the appropriate size of the safety database for clinical trials of a new drug. Attached hereto as D's Exhibit BW is a true and correct copy of the FDA website posting regarding the meeting on February 12-13, 2001, Drug-Induced Liver Toxicity: A National and Global Problem at http:www.fda.gov/cder/livertox/default2001/htm. I came away from this conference with the impression that the FDA was saying that it didn't have all the answers, but that it was going to be scrutinizing all development compounds, and also marketed products, for potential liver toxicity. As a result, I thought that liver toxicity was an issue which Abbott had to be very aware of for all its products in development and very thorough in its preclinical and clinical assessments of the potential for liver toxicity for all such compounds. I did not, however, believe that anything reported or discussed at the February 2001 meeting affected my assessment of any of the particular drug development programs that Abbott had underway at that time.

12. Based on my experience in the pharmaceutical industry and in regulatory affairs specifically, it is my understanding that in some situations the FDA looks across a particular group of compounds that are related either by structure or by activity to determine whether that group of compounds behaves similarly. Thus, with regard to ABT-773, it was my understanding based on discussions with FDA that they wanted Abbott to assess whether ABT-773, as a ketolide antibiotic, had any of the QT or liver toxicity issues that had been experienced by other macrolides. However, the FDA typically approves (or disapproves) a compound based on the data that is generated about that particular compound during the course of its development. In my experience, FDA does not delay its approval of a particular compound because of a theoretical concern

about potentially harmful possible class effects that are not reflected in the clinical data specific to that compound. If subsequent, related products are later developed that have safety issues that were undetected during the development of the initial compound FDA may then require class labeling for all similar compounds, including the initial compound.

13. On November 20, 2000, I participated in a teleconference with the FDA regarding ABT-773. I was the senior PPD regulatory affairs representative on the call. After the end of the teleconference, I prepared an FDA contact report in order to inform my manager, the ABT-773 project team, and senior management, including Dr. John Leonard (to whom the project team reported) about what had occurred during the teleconference. I believe that, consistent with my custom and practice in preparing FDA contact reports, this contact report for November 20, 2000 is complete and accurate to the best of my knowledge. Attached hereto as D's Exhibit 580 is a true and correct copy of an email dated November 20, 2000 from me to John M. Leonard and others, attaching a true and correct copy of my FDA contact report of the same date.

14. As is reflected in D's Exhibit 580, the FDA requested the November 20, 2000 teleconference. Specifically, the FDA requested that Abbott conduct a two-week dog toxicology study to assess ABT-773's potential for QT prolongation and for liver toxicity. D's Exhibit 580 at ABBT0558682. The FDA representatives informed us that they were requesting this additional study based on certain information that they were not at liberty to share. As discussed above, it was my understanding that the FDA was concerned in general about the two issues of QT prolongation and liver toxicity for all new drugs, including anti-infectives. It was my understanding from the November 20,

2000 teleconference that the FDA wanted to be sure that Abbott evaluated these issues for ABT-773 in the way that they were recommending. Based on my experience, issues such as this sometimes arise during development.

15. The November 20, 2000 teleconference with the FDA took place before the End of Phase II meeting with the FDA scheduled for November 27, 2000. During the course of the November 20 teleconference, it became apparent to me that the FDA representatives on the call were unaware that Abbott had already begun certain of its Phase III studies for ABT-773. The FDA representatives stated that they were not expecting us to begin our Phase III studies until after the End of Phase II meeting, and asked us to suspend enrollment in those studies. As reflected in D's Exhibit 580 at page ABBT055883, I interpreted this FDA request to suspend enrollment to mean that the program was on "clinical hold with these studies," and stated that in the contact report for the November 20 teleconference.

16. One week later, at the November 27, 2000 End of Phase II meeting, which I attended along with other Abbott representatives, the FDA informed Abbott that the ABT-773 program was in fact not on clinical hold. Attached hereto as D's Exhibit 582 is a true and correct copy of my contact report for the November 27, 2000 End of Phase II meeting with the FDA. As I recorded in the contact report of the November 27 meeting I prepared and distributed to Abbott management, the meeting began with the lead FDA representative at the meeting, Dr. Janice Soreth, stating "in case there was some misconception regarding the result of the telecon held on 11/20/00, she wanted to say that the ABT-773 program was at this point not on clinical hold." *Id.* at ABBT205257. Consistent with my custom and practice, the November 27, 2000 contact report attached

hereto as D's Exhibit 582 is a true and accurate reflection of what occurred at the November 27 meeting with the FDA. Attached hereto as D's Exhibit 781 is a true and correct copy of an email, dated November 28, 2000, which I prepared and sent to PPD senior management, also accurately reporting, to the best of my knowledge, the November 27, 2000 meeting with the FDA. As I reported in my November 28 email, the End of Phase II meeting with the FDA "was generally successful," with the FDA stating that the program was no longer on clinical hold and that we may proceed with our Phase III trials. In addition, the FDA reiterated its request that Abbott conduct the dog toxicology study, but noted that it could be done concurrently with Phase III trials.

17. During the November 27, 2000 meeting with FDA, Abbott discussed, among other things, the ECG data from the ABT-773 Phase II studies. As reflected in my contact report, the FDA then "informed us that they have begun to ask for special population studies with drugs that show an effect on ECG's." D's Exhibit 582 at ABBT205258. I was already aware from my experience in the industry, publicly available reports and discussions with the FDA that QT prolongation generally was a prominent issue in late 2000 and I understood that the FDA was looking to define how best to assess all drugs in development, including anti-infectives. I did not understand the FDA's request for this study to indicate that they had any specific concerns with regard to ABT-773.

18. It is my understanding that the burden is always on the sponsor of a drug under development to demonstrate safety, regardless of what the product is or what the FDA requests. However, I did not believe during the time I worked on ABT-773 that the regulatory requirements or challenges Abbott faced with regard to ABT-773's safety

profile for QT prolongation or liver toxicity were out of the ordinary or different than for any other compound under development or for any particular issue that the FDA has identified as being of interest regarding safety. With every drug, the sponsor has to provide data to the FDA (or other regulatory agency) to convince the Agency that the product is effective and that the benefits of the product outweigh the risks associated with the product's use. My understanding of the effect on the ABT-773 program of FDA's general concern about the potential for QT prolongation in anti-infectives, including macrolides and ketolides, was that Abbott would have to do a good job of evaluating the QT prolongation potential of ABT-773 and would have to provide FDA with enough information to convince them that ABT-773 did not have a QT prolongation concern. I had no reason to believe at the time I worked on the ABT-773 project that Abbott could not satisfy that requirement with regard to ABT-773. No one at Abbott indicated to me at any time that they had a contrary view of the FDA's views or actions, as they applied to the prospects for the development of ABT-773, or that they believed that Abbott could not successfully demonstrate that ABT-773 did not have a clinically significant QT prolongation effect.

The FDA's Pediatric Rule and ABT-773

19. In the course of my work in the PPD Regulatory Affairs department, I became familiar with the regulatory requirements for pediatric products, including pediatric indications and formulations for drugs originally developed for adult use. It is not unusual for the development of pediatric indications and formulations for drugs meant primarily for adult use to lag behind the development of the product for adult use. In part, this is because, as the FDA recognizes and takes into account in its application of

the pediatric rule, compounds under development are usually not tested in children until they have been shown to be safe and effective in adults. Under the pediatric rule, drug sponsors must either develop a pediatric formulation and conduct studies in children or obtain a waiver of this requirement by demonstrating to the satisfaction of the FDA that the drug is not expected to be safe for use in children or there are multiple safer options for children, the drug addresses a disease that is not present in children or is significantly different in children, or a pediatric formulation cannot be developed for the compound. If the sponsor does not yet have a pediatric formulation or has not conducted clinical studies in children at the time the sponsor seeks FDA approval of its adult formulation, or cannot yet make a showing sufficient to obtain a waiver of the pediatric rule's requirements, the sponsor can request a deferral of the requirement to conduct studies in children, until such time as adequate information is generated to support clinical studies in children. It is not the FDA's purview to assess the adequacy or timing of funding for development of a pediatric formulation or conduct of pediatric clinical studies. Rather, their concern is whether the sponsor can meet the requirements for waiver, deferral or a pediatric submission at the time the adult application is filed. If the sponsor obtains a waiver from the FDA or a deferral to allow it to complete development of the product for children at a later time, the FDA would approve an adult formulation of the drug without requiring the sponsor to complete the pediatric development by the time the adult product is approved. To my recollection, in my experience at Abbott with the products I worked on, FDA has not denied an NDA approval for failure to satisfy the pediatric rule requirements.

20. It was my understanding in late 2000 and in the first quarter 2001 that the ABT-773 program included a pediatric component, that some work on the pediatric

formulation work had already been performed, and that further studies were being planned. I had no doubt at that time that Abbott would either be able to satisfy the requirements of the pediatric rule by the time it submitted its request for approval of the adult formulation of ABT-773 to the FDA, or that Abbott would be able to obtain a deferral of those requirements at that time.

21. At no time during the period that I worked on ABT-773 did I believe, based on my knowledge of and experience with the FDA and the pediatric rule, that an adult formulation of ABT-773 would be rejected or held up by the FDA on the grounds that Abbott had failed to fulfill the requirements of the pediatric rule. I was confident that the fact that the pediatric formulation was not proceeding as quickly as the adult formulation would not prejudice Abbott's prospects for FDA approval of the compound. No one at Abbott ever indicated to me that they had a contrary view.

The FDA Advisory Committee Meeting to discuss Ketek

22. I recall that an FDA Advisory Committee was held to discuss the data available for Ketek, a ketolide antibiotic being developed by Aventis, in late April 2001. At this Meeting the Advisory Committee voted against approval of Ketek for the indications of chronic bronchitis and acute sinusitis, and did not address Ketek's pharyngitis indication. In addition, the Committee stated that Ketek needed additional data on QT prolongation and hepatotoxicity prior to receiving FDA approval for community acquired pneumonia (CAP). I reviewed publicly available reports about the recommendations of the FDA Advisory Committee and discussed them with members of the ABT-773 project team at the time, including the Head of the Anti-Infective Venture, Dr. Stanley Bukofzer. Attached hereto as D's Exhibit AC is a true and correct copy of an email attaching a

publicly available report of the FDA Advisory meeting about Ketek that I sent to Dr. Bukofzer and other Abbott employees, dated April 27, 2001.

23. Prior to the FDA Advisory Committee Meeting to discuss Ketek in late April, I had expected that FDA's concerns with regard to Ketek would be focused primarily on efficacy issues, rather than safety issues. However, as discussed in the April 27, 2001 Health News Daily Article attached to my April 27 email, the advisory actually focused to a large extent on the need for additional Ketek data on QT prolongation and hepatotoxicity.

24. Based on my experience and knowledge of the FDA's policies and practices during my career at Abbott, I knew prior to the FDA Advisory Committee Meeting about Ketek that FDA would require Abbott to show that ABT-773 was safe and effective. I was also aware that Abbott would need to have a large ABT-773 safety database in order to demonstrate safety to FDA's satisfaction. However, based on my experience with and knowledge of the FDA, as well as on my communications with my colleagues in Regulatory Affairs, it was not clear what size safety database the FDA would require to establish that QT prolongation and liver toxicity were not significant issues for ABT-773 or other ketolide antibiotics. Nor was it clear what number of resistant isolates would be required to satisfy the FDA that a resistance claim was warranted.

25. After the FDA Advisory Meeting on Ketek, it became clear from the results of the meeting that were widely publicized and from the transcript of the Advisory Meeting that was made available to the public that the FDA would be expecting sponsors of anti-infectives, especially macrolide and ketolide anti-infectives, to have much larger safety databases than were previously thought necessary by Abbott. In other words, the FDA

would expect very large numbers of patients in the safety database and a very low incidence of serious adverse events. Based on the publicly available information I reviewed after the FDA Advisory on Ketek, as well as on my discussions with members of the ABT-773 project team, including Dr. Bukofzer, and others during the period following the Advisory Meeting, it is my understanding that this view of the impact of the outcome of the Advisory Meeting on Ketek was widely shared at Abbott and across the pharmaceutical industry as a whole. In sum, the Advisory Meeting on Ketek was the first real public discussion of what we saw as a significantly increased regulatory hurdle for safety, in terms both of greatly increased patient numbers and of not having serious adverse events ascribed to the drug.

26. In June 2001, I reviewed and commented on a draft slide presentation prepared by members of the ABT-773 project team which discussed, in part, the effect of the FDA Advisory Meeting on Ketek on the development of ABT-773. Attached hereto as D's Exhibit 799 is a true and correct copy of this June 18, 2001 slide presentation. It was my understanding, based on my discussions with other members of the ABT-773 team, including Dr. Bukofzer, that the slides were planned to be part of a presentation to Dr. Leiden on ABT-773. I agreed with Dr. Bukofzer's assessment at page ABBT203854 of the presentation that "The Ketek advisory raised the [regulatory] hurdle for the approval of ketolides". I also agreed with the points made in the presentation that the FDA Advisory Meeting on Ketek indicated that FDA would require a much larger safety database and a greater number of resistant isolates than the ABT-773 project team had previously contemplated in order for the compound to receive regulatory approval and for a resistance claim to be granted. *See id.* at ABBT203854-203855.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this affidavit is executed this 15 day of February, 2008, at Abbott Park, Illinois.

Jeanne M. Fox

CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

/s/ Eric J. Lorenzini
Eric J. Lorenzini (*pro hac vice*)

AC

Jeanne M Fox
04/27/01 07:15 AM

To: Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT, Eugene X Sun/LAKE/PPRD/ABBOTT@ABBOTT, Stan Bukofzer/LAKE/PPRD/ABBOTT@ABBOTT, Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT, Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Tim Vanbiesen/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: FYI - Ketek

----- Forwarded by Jeanne M Fox/LAKE/PPRD/ABBOTT on 04/27/2001 07:14 AM -----

FDC Reports
Pink, Tan, Gray Sheets

NewsEdge

HEALTH-NEWS-DAILY

HLTHND: Health News Daily — April 26, 2001 Thursday

Aventis' Ketek Needs Additional Safety Data Before Approval For CAP, Cmte Says

HEALTH-NEWS-DAILY , April 27, 2001, Page 4

Aventis' Ketek (telithromycin) needs additional data on QT prolongation and hepatotoxicity prior to approval for community acquired pneumonia, FDA's Anti-Infectives Advisory Committee said April 26.

The committee recommended in a 7 to 3 vote that FDA approve the antibiotic for community acquired pneumonia, which is one of four indications being sought by the company.

Committee members voted unanimously against approval of Ketek for acute exacerbation of chronic bronchitis. Members questioned whether the benefit of Ketek would outweigh the risk in this population, given the availability of alternative therapies.

The committee also voted 8 to 2 against approval of Ketek for acute sinusitis, citing similar concerns.

The fourth indication Aventis is seeking for Ketek, tonsillitis/pharyngitis, was not addressed by the committee.

FDA statistician George Rochester, PhD, expressed concern with the risk/benefit ratio of telithromycin for tonsillitis/pharyngitis, noting that it is a mild disease, and the target population is typically children. Aventis' Ketek application includes data in patients 13 and older.

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BW

Liver Toxicity

Drug-Induced Liver Toxicity

Serious harm to the liver caused by drugs, and by the combination of drugs and oth substances is an important public health problem. As Americans ingest combinatio of prescription and over-the-counter drugs, herbal remedies, dietary supplements a alcohol, the possibilities for harm and liver injury increases. Many of these produc are chemicals that are processed and detoxified by the liver. These chemic processes may produce substances that injure liver cells in some people and result impaired liver functioning.

Although such adverse reactions are uncommon, they may be very serious and cau the sudden onset of liver failure or even death. Among patients with acute liv failure evaluated at liver transplantation centers in the United States, ingestion drugs has become the leading cause for liver failure, exceeding all other caus combined. Serious drug-induced liver injury is also the leading single cause f withdrawal of drugs from the market.

This web site includes the study documents, program, and presentations made at tl conference "Drug-Induced Liver Disease: A National and Global Problem", he February 12-13, 2001, in Chantilly VA. The conference was co-sponsored by tl Food and Drug Administration (FDA), the Pharmaceutical Research a Manufacturers of America (PhRMA), and academic consultants in liver disea represented by the American Association for the Study of Liver Diseases (AASLD).

Organizing and presenting this conference was not intended as an end in itself. It w meant to initiate in the public arena continuing cooperative efforts to identify a define the issues, to develop and agree upon research agendas, and to educa physicians and patients. Future postings at this web page includes presenting resul of the workshop discussion groups, and proposing research and educational work be done.

We encourage you to contribute your ideas about this topic. Please send yo comments to seniorj@cder.fda.gov.

Drug-Induced Liver Injury: A National and Global Problem
12-13 February 2001, Westfields Conference Center, Chantilly VA

Final Program

White Papers (Pre-Conference Study Documents)

- Pre-Clinical: Nonclinical Assessment of Potential Hepatotoxicity in Ma
- Clinical
- Postmarketing Considerations

Invited Presentations

Monday, February 12, 2001

Opening talks - Overview

- Welcome, Program Structure, Goals of the Conference and Workshop
  John Senior, MD, Food & Drug Administration (FDA)
- Drug-Induced Liver Injury Impacts on the Food and Drug Administration (FDA)
  Robert Temple, M.D., Associate Director for Medical Policy
  Center for Drug Evaluation and Research, FDA
- Impact of Hepatotoxicity on the Pharmaceutical Industry
  Bert Spilker, Ph.D., M.D., Senior Vice President, PhRMA, Washington, D.C.
- Impact of Drug-Induced Liver Injury on Hepatology and the Practice of Medicine
  William M. Lee, MD, Professor of Medicine, University of Texas Southwestern
  Medical Center

State-of-the-Art Presentations

- Pre-Clinical Issues in Drug Development
  François Ballet M.D., Ph.D., Aventis, Paris
- Clinical Picture and Issues in the Clinical Phases of Drug Development
  Neil Kaplowitz, M.D., University of Southern California, Los Angeles
- Post-Marketing: State of the Art and Issues Defined
  Peter K Honig, MD, MPH, Director, Office of Postmarketing
  Drug Risk Assesment, FDA

Tuesday, February 13, 2001

Current Topics in Hepatology

- How are these problems being addressed in Europe?
  Roger Williams, Professor of Hepatology, Institute of Hepatology, University
  College, London
- Looking for hepatotoxicity, working up patients, and assessing causality
  James W. Freston, M.D., Ph.D., University of Connecticut Health Center,
  Farmington, CT
- Emerging Trends in Acute Liver Failure in the United States
  William M. Lee, MD, University of Texas Southwestern Medical Center

- Pharmacogenomics: Dangerous drug or susceptible patient?
  Paul B. Watkins, M.D., University of North Carolina at Chapel Hill, NC

Back to Top Back to Liver Toxicity

FDA/Center for Drug Evaluation and Research
Last Updated: May 24, 2001
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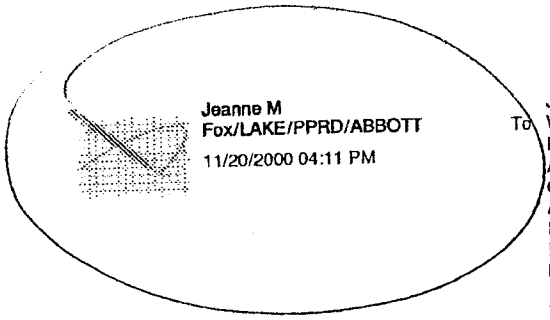
HTML by SJW



Jeanne M Fox/LAKE/PPRD/ABBOTT
11/20/2000 04:11 PM

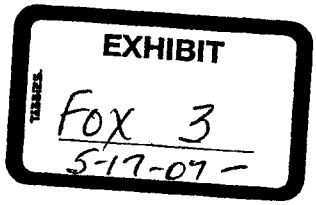
To: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Jerald J Wenker/LAKE/PPD/ABBOTT@ABBOTT, Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT, Arthur J Higgins/LAKE/PPD/ABBOTT@ABBOTT, Carl Cralt/LAKE/PPRD/ABBOTT@ABBOTT, George Aynilian/LAKE/PPRD/ABBOTT@ABBOTT, Reid Patterson/LAKE/PPRD/ABBOTT@ABBOTT, Julia Y Hui/LAKE/PPRD/ABBOTT@ABBOTT, William M Bracken/LAKE/PPRD/ABBOTT@ABBOTT, Maria M Paris/LAKE/PPRD/ABBOTT@ABBOTT, Joaquin M Valdes/LAKE/PPRD/ABBOTT@ABBOTT, David D
cc: Morris/LAKE/PPRD/ABBOTT@ABBOTT, Jie X Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Robert K Flamm/LAKE/PPRD/ABBOTT@ABBOTT, Linda E Gustavson/LAKE/PPRD/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT, Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Linda J Swanson/LAKE/PPRD/ABBOTT@ABBOTT, Cheryl D Spencer/LAKE/PPRD/ABBOTT@ABBOTT
bcc:
Subject: FDA Telephone Contact Report ABT-773

Attached is a contact report for a teleconference that was held with FDA today concerning ABT-773. We are now officially on clinical hold until further discussion at the End-of-Phase 2 meeting scheduled for November 27, 2000.

Call me if you have questions,

jeanne

FDA Contact Reportdoc.dc



FDA Contact Report

Compound/Product Discussed: ABT-773 Date of Contact: November 20, 2000
Application Type & Number: IND 57,836

	Name & Title	Group
FDA Person(s) Contacted	Dr. Janice Soreth, Acting Division Director	Division of Anti-Infective Drug Products
	Dr. Mercedes Albuerne, Supervisory Medical Officer	
	Dr. Alma Davidson, Medical Officer	
	Dr. Bob Osterberg, Supervisory Pharm/Tox Reviewer	
	Dr. Terry Peters, Pharm/Tox Reviewer	
	Maureen Dillon-Parker, CSO	
Abbott Representatives	Jeanne Fox	Regulatory Affairs
	Greg Bosco	"
	Carl Craft	Venture
	George Aynilian	"
	Reid Patterson	Drug Safety
	Bill Bracken	"
	Julia Hui	"

Subject of Call: FDA requested this teleconference to talk about some "toxicology issues" prior to our End-of-Phase 2 meeting scheduled for next week (November 27, 2000).

Report of Call: The meeting began with introductions, then Maureen said she was filling in for our CSO, Jose Cintron, and asked if we had been told the subject of the call. I told her we understood the purpose to be tox, but had no specifics. Dr. Peters then began by saying that she reviewed our 3 month monkey toxicology study as well as the inspection report and has several concerns about the study. First, there is a concern because the FDA investigator found that there was active drug in some of the control samples. Second, they have knowledge which they cannot share with us regarding similar drugs that has convinced them that the monkey is not a sensitive enough species to look for the two primary toxicities they are worried about with macrolides and ketolides, hepatotoxicity and QT changes. They had advised us of their recommendation that we use the dog after the results of the one month monkey tox study, and now they are looking at a 3 month study in monkeys that they believe is flawed. Reid explained the rational behind not using the dog since our early work in dogs indicated that emesis became so pronounced in dogs that we were unable to reach significant drug exposures, therefore we switched to monkeys. They asked whether we had done QT assessment in this study and we responded no, that our QT evaluation was done by the safety pharmacology group. They responded that they were looking for QT assessment on multiple dosing in toxicology studies, not the kind of information that came out of single dose pharmacology studies. They then stated that to meet the requirement to start phase 3, they need chronic toxicology done in two species and so they want us to do a 30-day dog study with full QT assessment done by telemetry and evaluation for hepatotoxicity. I pointed out that we have provided in our pre-meeting package specific analyses of both our hepatic safety evaluations and our QT monitoring results from the 900 plus patients that we have treated in Phase 1 and 2. Reid stated that since nothing significant was seen in any of the human data it would seem somewhat meaningless to go back and do the dog study. FDA asked to put us on hold.

When they came back after 5 minutes they said they would propose a compromise, and instead of a 30 day study, they would require a two week dog study with special emphasis on hepatotoxicity and QT, with telemetry and with a

recovery period. We agreed that it may be possible to run such a study, although we still have concerns about getting adequate exposures in the dog. I then said that our bigger concern was allowing this tox request to delay our phase 3 studies, and asked if it would be acceptable to run the tox study concurrently since the Phase 3 studies had already started. Based on FDA's reaction it was clear they were unaware that we have begun our studies. Dr. Soreth asked how we could do that prior to our end-of-phase 2 meeting. I pointed out that we had first requested a meeting in July, and it has been scheduled and rescheduled several times. I referenced the letter I sent to her in October when they cancelled the scheduled meeting the last time, which told her we would begin our trials the second week in November. I also referred to the new protocol amendments that were submitted over the last several weeks initiating the studies. She said they expected us to send the protocols to them and wait for comments before proceeding. I explained that we have received comments on at least one of the protocols and parts of the others. She wanted to know if our recent submissions stated we were planning to enroll patients now. I responded that these are our standard study start-up submissions that include information on a minimum of one investigator who can then enroll patients. I explained that we have several patients currently enrolled. Dr. Soreth was not happy with this information, and FDA put us on hold again.

When FDA came back off hold Dr. Soreth told us that they were not expecting us to begin our phase 3 studies prior to the end-of-phase 2 meeting, and that they want us to suspend enrollment at this time. In other words, we are now on clinical hold with these studies. They will discuss this information further prior to the meeting next Monday. I asked whether the 1 hour that has been allotted us next Monday will be enough. Dr. Soreth responded that it will have to be. She indicated they are probably still going to require a dog study. I commented that we do have in writing from Dr. Peters that the three-month study in monkeys should be acceptable to fulfill the requirement. We received this in response to our argument against using dog when they first raised it last year. They did not have the reviewers document in front of them, and Dr. Peters could not recall it, so they said they would go back and look through their records, She also stated that regardless, they would still have issues with the quality of the 3 month study. Reid promised to provide a written response to the issue of active drug in control samples, stated again that there was nothing significant enough to invalidate the study, and questioned whether we could get the exposures they were looking for in dogs. Dr. Peters commented that other sponsors with drugs like these manage to do dog studies. We agreed to provide an estimated timeline for a two-week dog study at Monday's meeting.

We suggested to Dr. Soreth that they also review the QT and hepatic safety assessments that were done in phase 2 since those were done at doses up to 600 mg, so there is more exposure in those phase 2 studies than we will have in phase 3. She said they will look at it.

Action Items: Provide a chronology showing all of the delays in getting the phase 2 meeting to happen as well as the submission of the protocols for review and the response from Dr. Peters acknowledging the 3 month monkey study as acceptable. Prepare a written response regarding the positive study drug in controls from the 3 month tox study.

582

FDA Contact Report

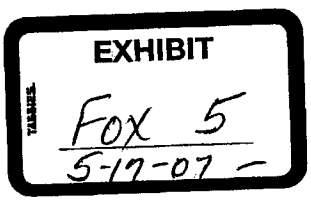
Compound/Product Discussed: ABT-773 - End of Phase 2 Meeting

Application Type & Number: IND 57,836 Date of Contact: November 27, 2000

	Name & Title	Group
FDA Person(s) Contacted	Jose Cintron, Sr. Project Mgr	Anti Infective Division
	Mercedes Albuerne, Medical Team Leader	"
	Nasim Moledina, Medical Officer	"
	Mamodikoe Makhene, Medical Officer	"
	Alma Davidson, Medical Officer	"
	Daphne Lin, Statistics Team Leader	"
	Erica Brittain, M.D., Statistics Reviewer	"
	Terry Peters, Pharm/Tox Reviewer	"
	Robert Osterberg, Pharm/Tox Team Leader	"
	Lilian Gavrilovich, Deputy Director	"
	Charles Bonapace, Biopharm Reviewer	"
	Frank Pelsor, Biopharm Team Leader	"
	Sousan Altaie, Micro Reviewer	"
	Jean Mulinde, Medical Officer	"
	Jim Timper, Chemistry Reviewer	"
	Charles Cooper, Medical Officer	"
	Albert Sheldon, Micro Team Leader	"
	Janice Soreth, Acting Division Director	"
	John Alexander, Medical Officer	"
	Diane Murphy, Office Director	Office of Drug Evaluation - IV
Abbott Representative(s)	Greg Bosco, Sr. Product Mgr	Regulatory Affairs
	Jeanne Fox, Director	Regulatory Affairs
	Jie Zhang, Statistician	Clinical Statistics
	Joaquin Valdes, Physician	Anti Infective Venture
	Carol Meyer, Operations Manager	Anti Infective Venture
	Bob Flamm, Microbiologist	Microbiology
	Linda Gustavson, Pharmacokineticist	Clinical Pharmacokinetics
	David Morris, Statistician	Clinical Statistics
	Maria Paris, Physician	Anti Infective Venture
	George Aynilian, Associate Venture Head	Anti Infective Venture
	Carl Craft, Venture Head	Anti Infective Venture
	John Leonard, Vice President	Research & Development
	Reid Patterson, Vice President	Drug Safety

Subject of Meeting:
The purpose of the meeting was to introduce the oral tablet Phase 3 development plan, discuss potential issues, and address any questions regarding the plan or Phase 2 study results.

Report of Meeting:
The meeting began with introductions from both sides. As Carl began his presentation, Dr. Soreth stated that in case there was some misconception regarding the result of the telecon held on 11/20/00, she wanted to say that the ABT-773 program was at this point not on clinical hold.



Carl began his presentation with a slide showing the proposed indications and treatment durations we were planning to file in the NDA. He showed a series of slides which summarized all the Phase 3 studies we are planning; those starting in 2000 and those slated for 2001. This was the first time FDA saw the proposed dose-selection studies for pneumonia (CAP) and sinusitis (ABS). Dr. Brittain had a few questions regarding the objectives of the studies and the proposed interim analyses, but stated that she would be faxing us all of her comments in more detail. Carl stated that the objectives of the studies were: to pick a dose for the large, well-controlled, comparative, pivotal studies to be conducted in 2001, and to meet the specific pathogen criteria as required for the second supportive trials in the FDA guidance for CAP and ABS. There was lengthy discussion around these study designs. It was stressed to FDA that we still intend to conduct a large, well-controlled, double-blind, comparative trial for each of these indications. FDA advised us there might be a problem using Augmentin 875 mg BID for the sinusitis trial. They would prefer us to use 500 mg TID. Carl committed that we would provide the results from these two trials to FDA for review.

The next slide shown detailed our intention to request a claim for macrolide and penicillin resistant bacteria and atypical bacteria, and the supporting data we proposed to provide to support these claims. Dr. Albuerne stated that we could pool isolates for CAP and ABECB but not for ABS (we proposed pooling from all three). Dr. Soreth stated that there is currently no guidance document available addressing specific requirements for resistant claims but mentioned that there is data from other products (e.g. levofloxacin) that is available in the public domain. As far as our proposal for number of isolates, numbers >10 would be acceptable with good data for susceptible pathogens, but there has been an instance (with linezolid) where <10 was not approvable, but in that case only one or two patients had bacteremia and responded well to therapy. It was stated that a number of bacteremic patients would be required in order to adequately evaluate clinical success against penicillin resistant *Strep pneumoniae*. The comment was made that with oral therapy alone we would probably be hard pressed to find enough patients with bacteremia, that oral/IV therapy gave us a better chance. Dr. Soreth stated that FDA has not seen data supporting "macrolide resistant *Strep pneumoniae*" as a clinical concern. They also said that there is no good body of evidence supporting macrolide resistant *Strep pyogenes* either.

The next topic discussed was the ECG monitoring plan regarding the six Phase 3 studies starting in 2000. We proposed that ECG's would be performed in 5/6 of the studies. In total, we would be gathering ECG data on ~2000 subjects exposed to ABT-773. ECG's will be performed pre-, during, and post-therapy. Additionally, the timing of the ECG and the timing of the dose before the ECG will be documented. FDA requested that we amend all informed consents to mention possible effects on cardiac repolarization caused by ABT-773. Various examples of wording was then discussed and we agreed that we would amend the informed consents for all IND studies. Dr. Soreth asked why we were not doing ECG's in the sixth study. Carl stated that the European pharyngitis study would not include ECG's based on recommendations of our European advisors based on the number of existing visits and the likelihood of subject reluctance to participate in a trial for this disease with so many visits. FDA strongly disagreed with this justification. Dr. Murphy expressed concern that we were blatantly misinforming the subjects in that trial by not including a procedure that would monitor a potentially serious adverse event that was being included in all other studies. This issue was left unresolved. Other comments regarding the collection of a blood sample taken at the on-therapy ECG, etc. were made. All issues were addressed in a subsequent written correspondence by FDA (faxed 12/5/00, Abbott response 12/14/00).

Relating to the topic of possible adverse effects on cardiac repolarization, the results of the previously submitted toxicology studies were discussed. Dr. Peters requested additional data in the dog model. The requested study should be a two-week acute study with telemetry and the study can run concurrent with the Phase 3 clinical trials. At this point Reid offered to provide some background information. He indicated that the emetic activity of ABT-773 in the unanesthetized dog limits exposure in this species, leading to our selection of the cynomolgus monkey as the non-rodent model. While the primate did not indicate a risk for QTc prolongation, exposures of 17 times the human Cmax in anesthetized dogs did lead to some prolongation. Owing to differences in protein binding, the dog receives about 3 times the amount of unbound drug than does the human with identical exposures, perhaps expanding our margin of safety. Various proposals for the study were discussed between Reid and Drs. Peters and Osterberg. We committed to sending draft protocols to Dr. Peters for review.

Carl briefly discussed the Phase 2 ECG data. Dr. Soreth informed us that they have begun to ask for special population studies with drugs that show an effect on ECG's. In this case they would be looking at a study in otherwise healthy subjects with underlying cardiovascular disease. She commented that only looking at the effects

of ABT-773 in comparator trials might not be realistic (i.e., cisapride and terfenadine looked safe in the clinic too). Dr. Murphy commented that it is in both of our best interests to get all the information we can to show how to use the drug safely.

The rest of the meeting was spent answering specific questions regarding the four main Phase 3 trials (CAP, ABS, ABECB & pharyngitis). Most of the comments related to minor protocol changes. All of the issues discussed were subsequently provided to Abbott by fax on 12/5/00. Abbott formally responded to the fax in IND 57,836, Serial No. 066, dated 12/14/00.

Action Items:

- Amend Phase 3 informed consents to incorporate statements relating to: possible effects on cardiac repolarization caused by ABT-773, possible interactions with other drugs, and stronger precautions for women of childbearing potential.
- Provide full narratives from Phase 2 studies of all patients who had an adverse event of syncope or elevated liver enzymes.
- Submit draft toxicology protocol(s) for comment prior to initiating the studies.
- Submit results from CAP and ABS dose-selection trials when available.
- Submit draft protocols for the two well-controlled, comparative, pivotal studies for CAP and ABS (to be conducted in 2001) for comment as soon as available.

Jeanne M
Fox/LAKE/PPRD/ABBOTT
11/29/2000 01:48 PM

To: Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Carl Craft/LAKE/PPRD/ABBOTT@ABBOTT, George Aynillan/LAKE/PPRD/ABBOTT@ABBOTT
cc: Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT
bcc:
Subject: Slides for 12/5 meeting

OK, here's my first draft of slides for the Leiden meeting. Please feel free to make comments or redirect me if you think I'm missing something. I guess I think after our meeting on Monday, the only major issues identified which are still open are QT, liver, and resistant pathogens, so that's what I focussed on with some general comments at the end.

jeanne

p.s I apologize for the separate files. I am obviously not as good on my PC as Rod is

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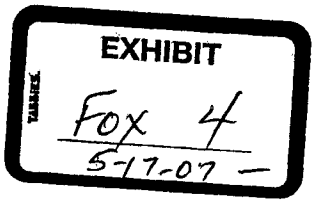


ABT-773 Regulatory Status

- Original U.S. Oral IND submitted 2/2/99
- Phase 3 pivotal trials initiated 11/00
- End-of-Phase 2 Clinical FDA meeting 11/27/00
- End-of-Phase 2 CMC FDA meeting target 1/01
- Tablet NDA submission target 8/02

ABT-773 Regulatory Issues

- ABT-773 Potential for QT Prolongation
  - QT issue is hot button for FDA
  - Question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QT
  - Required to include ECG monitoring in pivotal Phase 3 studies

ABT-773 Regulatory Issues

- ABT-773 Potential for QT Prolongation (continued)
  - telithromycin (Ketek) data residing at FDA
    - Advisory Meeting scheduled for January
- FDA may require a Phase 1 study in patients with underlying cardiac disease
- Some antimicrobials now contain warnings for QT prolongation

ABT-773 Regulatory Issues

- ABT-773 Potential for Liver Toxicity
  - Ketolides similar to macrolides?
  - Request for additional dog tox. work
  - telithromycin (Ketek) data residing at FDA
    - Advisory meeting scheduled for January
- Plan to conduct routine liver monitoring in all Phase 3 studies

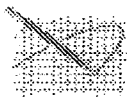
ABT-773 Regulatory Issues

- Indication to treat resistant pathogens
- FDA skepticism regarding clinical significance of "macrolide-resistant *S. pneumo*"
- FDA will require "body of evidence"
  - excellent eradication of susceptible organisms
  - > 10 resistant organisms eradicated to include good proportion of bacteremic CAP patients

ABT-773 Regulatory Issues

- Miscellaneous
  - Based on NDA timing, potential good candidate for E-submission
  - Timing of IV program may affect ability to document effectiveness vs. resistant pathogens in bacteremic patients
  - Timing of pediatric program and "due diligence" for formulation development critical

781



Jeanne M Fox/LAKE/PPRD/ABBOTT
11/28/2000 09:27 AM

To: Lawrence E Roebel/LAKE/PPRD/ABBOTT@ABBOTT, Jerald J Wenker/LAKE/PPD/ABBOTT@ABBOTT, Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT, Rod M Mittag/LAKE/PPD/ABBOTT@ABBOTT, Arthur J Higgins/LAKE/PPD/ABBOTT@ABBOTT, Linda J Swanson/LAKE/PPRD/ABBOTT@ABBOTT, Mike Rubison/LAKE/PPRD/ABBOTT@ABBOTT, Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT

cc: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Carl Craft/LAKE/PPRD/ABBOTT@ABBOTT, George Aynilian/LAKE/PPRD/ABBOTT@ABBOTT, Reid Patterson/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, Jie X Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Linda E Gustavson/LAKE/PPRD/ABBOTT@ABBOTT, Joaquin M Valdes/LAKE/PPRD/ABBOTT@ABBOTT, Maria M Paris/LAKE/PPRD/ABBOTT@ABBOTT, Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT

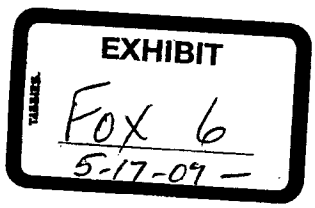
bcc:

Subject: Executive Summary of ABT-773 End-of-Phase 2 Mtg w/ FDA

Yesterday (11/27) the Abbott people on the CC list met with FDA's Anti-Infective Division for the End-of-Phase 2 meeting on ABT-773. Prior to the meeting we had been placed on clinical hold in a teleconference last Monday (11/20). Following are the high points from yesterday's meeting. Detailed minutes of the meeting will be distributed at a later time.

The meeting was generally successful. FDA stated that we are no longer on clinical hold and may proceed with our Phase 3 trials. They have requested additional toxicology work be done to evaluate QT in dogs, but the study can be done concurrently with Phase 3 and they will consider study design proposals from Abbott. FDA accepted the design for the CAP and sinusitis dose-selection studies, although they suggested changes to the statistical analyses for these studies. While FDA acknowledged that our proposal for 15 resistant isolates/pathogen to support a claim for resistant organisms looked reasonable, they will need a good, solid body of evidence. They cautioned us that they have not seen a body of data that supports macrolide resistant Strep pneumo as a clinical concern. They also advised us that we would need to include bacteremic CAP patients with resistant pathogens in order to secure an indication, which would be difficult to do with an oral drug. The FDA reviewers provided a number of recommended protocol changes, most of which are minor to actual study conduct. In addition, we were directed to modify all of our informed consents to inform patients that QT prolongation has been seen with related classes of drugs and therefore may be a risk with ABT-773.

jeanne



Stan Bukofzer /LAKE/PPRD/ABBOTT
06/22/2001 12:48 PM

To: Jeanne M Fox/LAKE/PPRD/ABBOTT@ABBOTT
cc:
bcc:
Subject: Re: Please read. Final copy of 773 decision analysis planned presentation to Jeff.

Jeane thanks for all your insights and the effort you put into the review. I guiess that we are in total agreement and understanding of all the issues.They are just not expressed adequately.
Slide 2 -agreed, I had expressed it badly.
slide4 This is not for the indication, but the 1 component of the iv dose.By time I meant in respect of the filing of tabs.(if we can use it only for the bugs,....another assumption that we would say use 2 iv doses and then convert to oral...)
slide 6. great this helps the decision.
allthe others...staed badly on the slide...only in the time frame of the oral submission. We need a full large comparative study for the IV submission as awhole in addition to all of this\
thanks
stan

Jeanne M Fox

Jeanne M Fox
06/18/01 09:02 AM

To: Stan Bukofzer/LAKE/PPRD/ABBOTT@ABBOTT
cc: Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Eugene X Sun/LAKE/PPRD/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT, Jennifer J Moore/LAKE/AI/ABBOTT@ABBOTT, Keith F Hendricks/LAKE/AI/ABBOTT@ABBOTT
Subject: Re: Please read. Final copy of 773 decision analysis planned presentation to Jeff.

Stan,

I reviewed the slides carefully and have the following comments/suggestions.

Slide 2: You state that "FDA did not exlicitly address resistance" for Ketek. I would suggest we say "it is unknown but doubtful, that Ketek will receive a resistance claim." I believe the approvable letter probably tells them where they stand on resistance but since they didn't say anything in their press release, we just don't know.

Slide 4: Regarding the IV step down program, you state that you will have a multiple dose study and a 300 patient open study. When we discussed this, I believe I suggested that we will need a large comparative blinded study AND an open label non-comparative study. Just 300 patients on IV step-down will not get us approved. Also, you say that these studies are non-time sensitive, did you mean they are non-season sensitive since severe CAP happens all year long?

Slide 6: QD in the US & BID in the EU is still not a viable program from a US regulatory standpoint if we select this choice today.

Slide 8 and 28-29: This again states that we will do one Phase III IV study. That will not get us approval, we will need two studies minimum, one double blind comparative and one open label noncomparative. Slide 30 very clearly states that we will need the two IV step-down studies, so perhaps it just got left off Slide 4, 8, 28-29.

That's all, no comment on the rest.

EXHIBIT BUKOFZER 15 5/9/07
PENGAD 800-631-6989

Good Luck, we're very anxious to hear how it goes!

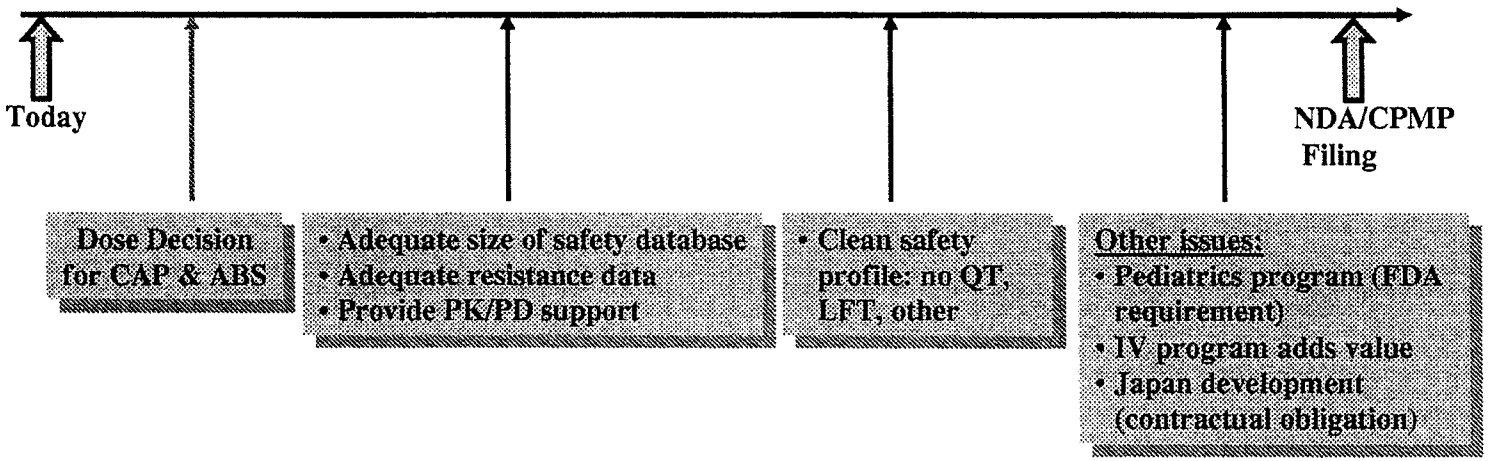
jeanne
Stan Bukofzer

Stan Bukofzer
06/17/2001 07:46 PM

To: Eugene X Sun/LAKE/PPRD/ABBOTT@ABBOTT, Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Keith F Hendricks/LAKE/AI/ABBOTT@ABBOTT, Jennifer J Moore/LAKE/AI/ABBOTT@ABBOTT, Gregory Bosco/LAKE/PPRD/ABBOTT@ABBOTT, Jeanne M Fox/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: Please read. Final copy of 773 decision analysis planned presentation to Jeff.

Leiden Briefing v04 dose decision strategy18june 01

Filing date dependant on timing of Dose decision and Program size. Program size dependant on technical and regulatory hurdles



The Ketek advisory raised the hurdle for the approval of ketolides:

- Size of the safety database is driven by the product **benefit/risk** profile.
  - Ketek's 3700 patient safety database insufficient.
  - ABT773 benefit risk is different for QD/BID

- A US resistance claim will significantly support benefit risk;
  - based on clinical cure rate of resistant isolates, with an emphasis on bacteremic patients (CAP indication only). Usual ratio 3:1
    - Ketek submitted 17 PRSP and MRSP isolates with 85% clinical cure and 6 bacteremics with 64% clinical cure.Leavofloxacin successful with 15 isolates and 6 bactereamics:100% cure. 773 cure Ph 2 73% sputa isolates, no bactereamia.
    - The advisory committee voted against a resistance claim; the FDA did not explicitly address it

Isolates Needed	% CAP patients with PRSP/MRSP		
	1.4%	1.6%	3.2%
17	1236	1063	531
25	1818	**1563**	781
30	2182	1875	938

Current Phase 3 run rate 2% PRSP,supports CAP 1500 patients

Safety database size issues.

- After program: 500 CAP patients in pursuit of resistance claim

300 ABS patients (double-tap 150; Ph3 150):

Outcome*	Safety Database		No. CAP Pts		Estimated no. isolates (50th percentile)	
	Before	After	Before	After	Before	After
QD	4200	5000	1000	1500	17	25
BID	2400BID 1800QD	3050 BID 1950 QD	750	1250	13	21

Above assumes same dose ABS and CAP.

- Safety database needs more patients if BID dosing, not especially if QD.
- Could do so with sinusitis pats(less time critical), but CAP patients allow for pursuit of resistance claim.
- To optimise chance of resistance claim need IVI program.(pead program could not catch up in time)

Investment in an IV formulation may add significant value, especially for a BID dose.

- Contribute to CAP bacteremic patients and resistant isolate numbers and if step-down to safety numbers
- IV step-down studies can be run simultaneously with tablet studies:
  - Non-competitive and mostly non time sensitive
  - Increases the safety database by an additional 300 CAP patients.
- Depends on regulatory approval as different formulation.(50:50)
- Incremental cost of IV step-down $6MM (multiple dose study and 300 patient open label study). Total program $22MM
- IV commercial advantages:
  - Direct sales of IV formulation.
  - Sales resulting from step-down to oral.
  - Increased likelihood for formulary acceptance.
  - Enhances potency image.

Phase IIIa current blinded data – ongoing studies.

	Pats enrolled	last in	last out	dose decision
Sinusitis	441/500	early July	late Aug	late Oct
CAP	304/500	early Nov	early Jan,	mid Mar

Indication (CRFs)	Clinical Response in Ph III Studies		
	Cure	Failure	Indeterminate
ABS (212)	155 (79%)	42	15
CAP (164)	125 (90%)	14	25
ABECB (330)	253 (86%)	55	22
ASP (360)	294 (86%)	46	20

- **Bacteriological response Ph3:**
  - 54% pos isolates in CAP.
  - 28% SP
  - 4% MRSP, 2% PRSP
  - 1 bactereamia

Bacteriological cure rate *Phase II studies.*

863 patients sputa cultures

11 **PRSP**.

Cured 73% (8/11).

Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

Strategic Alternative	Description
Use ABS & CAP dose-ranging data	• Complete current ABS & CAP dose-ranging trials and then make dose decision. • Complete Phase III pivotal with selected dose.
Use ABS dose-ranging data only	• Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. • If QD succeeds in ABS, obtain regulatory approval for conducting QD CAP pivotal.
Select BID today	• Select the BID dose today for ABS & CAP Ph III pivotal. • Do not wait for completion of the dose-ranging studies.
Select QD Today	• Select the QD dose today for ABS & CAP Ph III pivotal. • Do not wait for completion of the dose-ranging studies. • US & EU regulatory non-viability.
QD in the US & BID in the EU	• Develop BID in CAP & ABS for EU; Develop QD for US. • Clinical program requires 3 simultaneous CAP comparator studies – unacceptable costs and timelines.
Phase III 3-arm CAP & ABS pivotal	• Expand the Phase III CAP program to allow for 3 arms per study – QD vs. BID vs. comparator. • Very high technical/statistical risk and defers dose decision.

The estimated NDA filing date is impacted by the timing of the QD/BID dose decision.

Dose Selection Strategy	Dose Decision Date	Phase III			NDA Filing	Delay from 08/02 (mo)
		Start	Finish	Months		
Use ABS & CAP dose-ranging data	Mar 02	Sep 02	Dec 03	16	Mar 04	20
Use ABS dose-ranging data only [1]	Oct 01	Jan02-Mar02	Jun 03 Aug 03	16	Sept 03	13
Select BID Today[2]	Jun 01	Sep 01	Dec 02 Jun 03	16-22	Mar 03-Aug 03	6-12

- **[1] QD outcome for ABS indicates technical feasibility for CAP but requires regulatory approval resulting in delay of startup.**
- **[2]Inclusion of an IV study extends only the "Select BID Today" option by an additional 6 months (IV is on critical path in this scenario).**

Extra CAP patients	6months
Dose decision/	3 months/8months
IVI (only BID today)	6months

The timing of the dose decision increases total nominal cost, and affects the annual spending pattern.

Program costs to date $300MM include $ 56MM spent YTD date. (1)

Costs	2001(1)	2002	2003	2004	Total	Exp Cost
Use ABS & CAP dose ranging data	$24.2MM	$28.3MM	$42.0MM	$27.1MM	$121.6MM	$101.6MM
Use ABS dose-ranging data only	$24.4MM	$40.3MM	$48.4MM	-	$113.1MM	$98.3MM
Select BID Today	$34.7MM	$49.1MM	$24.7MM	-	$108.5MM	$97.9MM
Current LRP	**$32.5MM**	**$61.3MM**	**-**	**-**	**$93.8MM**	**$86.9MM**
Incremental cost to complete IV program(2)	$1.0MM	$5.7MM	$6.2MM	$3.9MM	$16.8MM	$13.7MM

- (2) All options include one Phase III IV study ($6MM across 2002-2003).

A quantitative analysis was conducted to value each of the proposed strategic alternatives.

- The decision tree model incorporates a discounted cash flow based on:
  - Technical uncertainties
  - Regulatory constraints
  - Commercial risks and opportunities
  - Timing of cash flows

- Alternatives are ranked on the basis of expected net present value.

Several technical issues were assessed to evaluate the overall risk of the ABT-773 program.

Key Technical Assessments	Probability	
	150 mg QD	150 mg BID
Sinusitis (ABS): Probability of technical success	25%	65%
Pneumonia (CAP): Probability of technical success	65%	85%
Pharyngitis (ASP): Probability of technical success	70%	NA
Bronchitis (ABECB): Probability of technical success	80%	NA
Resistance claim: Probability of obtaining 25 resistant isolates (with IV program)	70%	50%
Resistance claim (MRSP & PRSP): Probability of clinical cure	60%	80%
QT Safety: Probability QT signal is "worse than Clari"	15%	50%
Hepatotoxicity: Probability LFT signal exceeds acceptable levels	15%	15%

- Additional technical uncertainties considered:
  - IV formulation: impact on probability of achieving resistance claim
  - Efficacy endpoints: probability of of partial clinical success in Phase III (less than four indications)
  - Tolerability: GI and taste occurrence

Regulatory and commercial risk were assessed to fully value each strategic alternative.

Regulatory Requirements	
US	**EU**
• Increased emphasis on CAP success to obtain regulatory approval of the drug. • **Split CAP/ABS dosing feasible.**	• Requirement for both CAP and ABS success to obtain regulatory approval of the drug. • **CAP & ABS ideally the same dose (either QD or BID).**
• Resistance claim increases the probability of approval, especially if there are safety concerns. • QD and BID doses are equally approvable, given technical success.	

Key Commercial Assumption	Peak Sales (% base)	
	US	EU
150 mg QD in all indications (at launch)	100%	100%
150 mg BID for CAP & ABS (at launch)	50%	79%
Launch with 150 mg BID for CAP & ABS – follow with QD line extension	60%	90%
Launch with a resistance claim (multiplier; QD / BID)	*1.32 / *1.10	*1.49

The optimum Phase III development program is a trade-off between launch timing, technical, regulatory and commercial risk.

Strategy	Dose	Filing Date	Prob Res Isolates Enrolled	Prob Safety Database Acceptable	Prob of Launch		Expected Value ($MM)		
					US	EU	US	EU	WW
Use ABS & CAP dose-ranging data	QD/BID	Mar 04	40-50%	75%	0.58	0.47	166	217	378
Use ABS dose-ranging data only	QD/BID	Sept-Nov 03	40-50%	75%	0.58	0.47	182	234	411
Select BID today ₣	BID	Aug 03	50%	75%	0.58	0.47	69*	241*	299*
Current Timeline	BID*	Aug 02	25%	10%	0.07	0.05	-56	-38	-94

•Includes optional Ph IV QD line extension.
•₣ includes IV timeline

- Given the key limiting factor of CAP patient recruitment, and the technical attributes of the drug, the only strategy identified to increase the probability of launch is the IV formulation.
- No strategies identified to decrease time to filing. Limitation is adequate patient recruitment from competant sites.

- **Team recommendations:**

Wait for the ABS dose-ranging data before making a dose decision:

- Highest expected value in the US and worldwide. The EU value is comparable to the next best option.
- The NDA filing date is the earliest possible, if ensure resistance numbers with IVI and if its acceptable to Regulatory agencies.
- Can include IV with no time penalty and cost of $6MM

Decision alogarithm with ABS outcome

Currently at 79% blinded clinical success QD/BID
Dose decision on ABS driven by stats: If 10% difference, choose (80%). If less choose dose >80%. If both are then
revert to numerical superiority of Clinical cure.

ABS

- **BID: EU needs same dose: BID ¶**
- **: EU can split dose : Await CAP QD or BID***
- **QD : Visit Reg Agencies to extrapolate to CAP : QD**

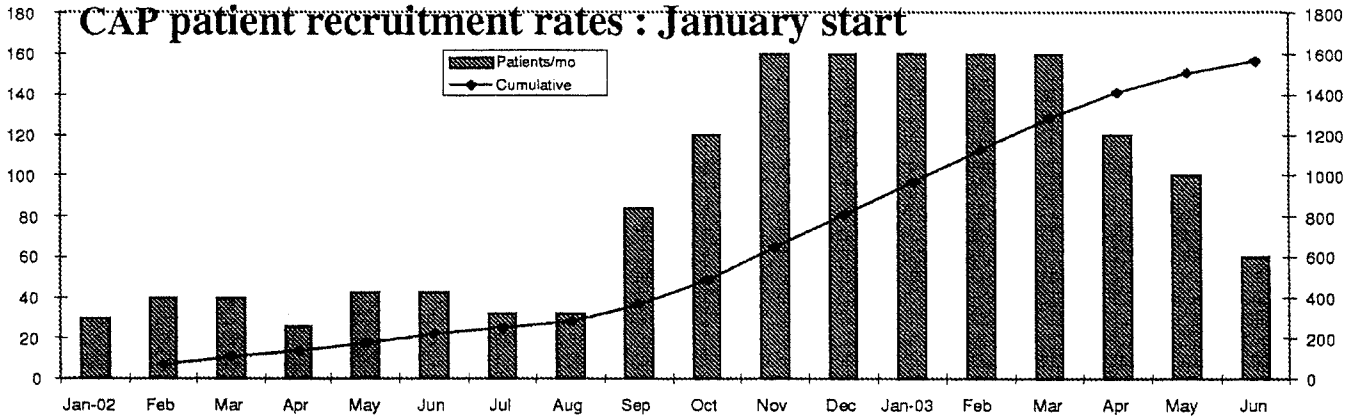
***option of waiting lower NPV**
¶ not viable to have separate dosing

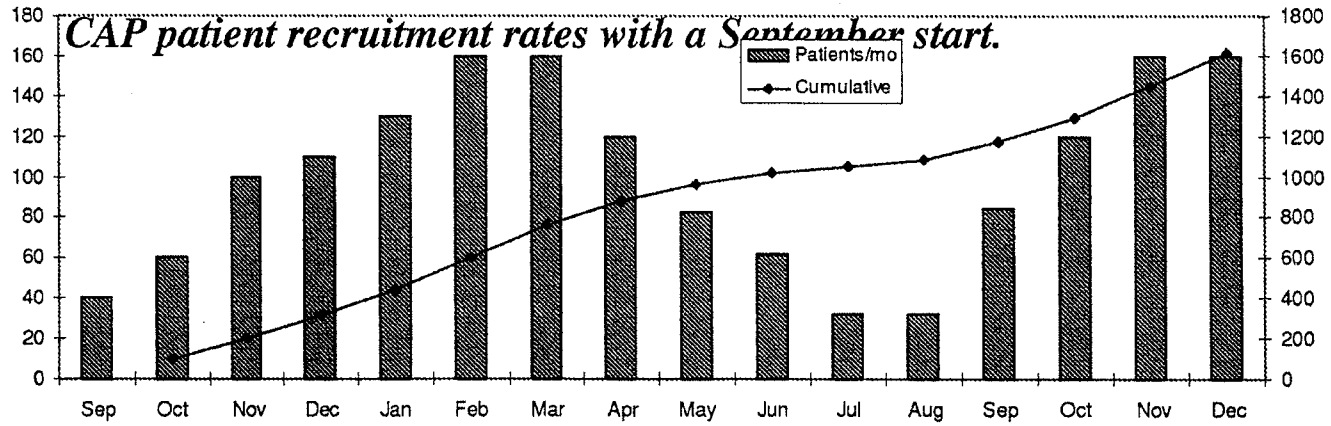
Immediate path ahead

- Prepare ABS and CAP trials for both doses so no time delay on decision.
- Ensure critical timeline of ABS dose decision-database lock dependant on CRF finalization.
- Continue to refine criteria for dose decision
- Ensure early meeting with Agencies to a priori investigate extrapolation of QD dose from ABS to CAP under pretext of QT trial.
- Ensure timelines of IVI program on track assuming funding.
- Rollover ABS (and CAP) into open label trials to ensure ongoing site participation.

Backups

1500 CAP patients require 16-18 months for enrolment

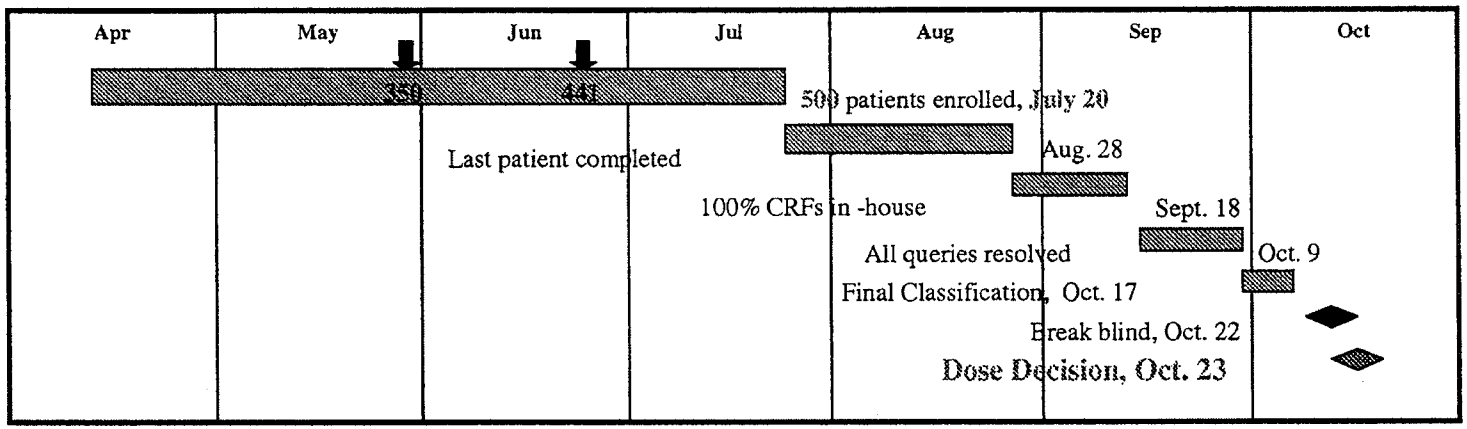




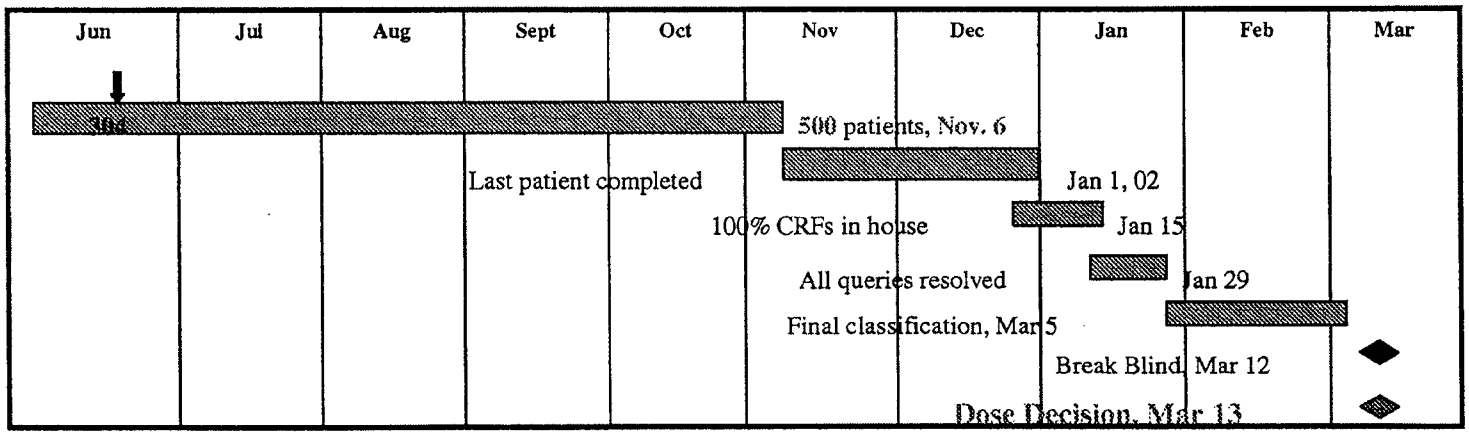
- **Extra 500 patients require 5-6 months**
- **Historical seasonality impact of about 2 months - depends on start Ph3**

Start of Ph3 trials and filing dates dependant on dose decision timeline.

M00-225:Sinusitis 150 mg QD vs. 150 mg BID



M00-219: CAP 150 mg QD vs.. 150 mg BID



PART 2

Ketek Clinical Trial Summary

AECB #1	Ketek 800 mg QD x 5d	Ceftin 500 mg BID x 10 d
Cure	89%	86%
Eradication	88%	86%
-S.pneumo	100%	75%
-H. flu	88%	85%
Diarrhea	11%	10%
Nausea	9%	3%
Dizziness	NS	NS
AECB #2	**Ketek 800 mg QD x 5d**	**Augmentin 500 mg TID x 10 d**
Cure	86%	82%
Eradication	69%	70%
AEs (combined)	24%	37%
Pharyngitis #1	**Ketek 800 mg QD x 5d**	**Biaxin 250 mg x 10 d**
Cure	91%	91%
Eradication	91%	89%
Diarrhea	17%	8%
Nausea	11%	4%
Dizziness	6%	1%
Pharyngitis #2	**Ketek 800 mg QD x 5d**	**Pen V 500 mg TID x 10 d**
Cure	95%	94%
Eradication	84%	89%
Diarrhea	12%	3%
Nausea	6%	1%
Dizziness	3%	1%

CAP #1	Ketek 800 mg QD x 10d	Biaxin 500 mg BID x 10 d
Cure	86%	89%
Eradication	89%	96%
-S.pneumo	94%	93%
-H. flu	78%	100%
Diarrhea	13%	7%
Nausea	9%	5%
Dizziness	4%	2%
CAP #2	**Ketek 800 mg QD x 7-10d**	**Trovan 200 mg QD x 7-10d**
Cure	91%	95%
Eradication	94%	100%
Diarrhea	17%(sig.)	6%
Nausea	8%	4%
Dizziness	2%	7%
CAP #3	**Ketek 800 mg QD x 7-10d**	**Amoxicillin 1 g TID x 10 d**
Cure	95%	90%
Eradication	88%	87%
-S.pneumo	96%	86%
-H. flu	75%	85%
Diarrhea	10%	8%
Nausea	8%	4%
Dizziness	NS	NS
CAP #4	**Ketek 800 mg QD x 7-10d**	**None**
Cure	93%	–
Eradication	89%	–
Diarrhea	8%	–
Nausea	5%	–
Dizziness	NS	–
Sinusitis #1	**Ketek 800 mg QD x 10d**	**Augmentin 500 mg TID x 10d**
Cure	74%	75%
Eradication	86%	75%
Diarrhea	20%	24%
Nausea	NS	NS
Dizziness	NS	NS
Sinusitis #2	**Ketek 800 mg QD x 5d**	**Ketek 800 mg QD x 10 d**
Cure	91%	91%
Eradication	91%	91%
-S.pneumo	93%	89%
-H. flu	100%	85%
Diarrhea	10%	13%
Nausea	5%	2%
Dizziness	NS	NS

Sinusitis #3	Ketek 800 mg QD x 5d	Ketek 800 mg QD x 10 d	Augmentin 500 mg TID x 10 d
Cure	75%	74%	75%
Eradication	86%	86%	75%
Diarrhea	19%	20%	24%
Nausea	12%	9%	8%
Dizziness	5%	5%	2%

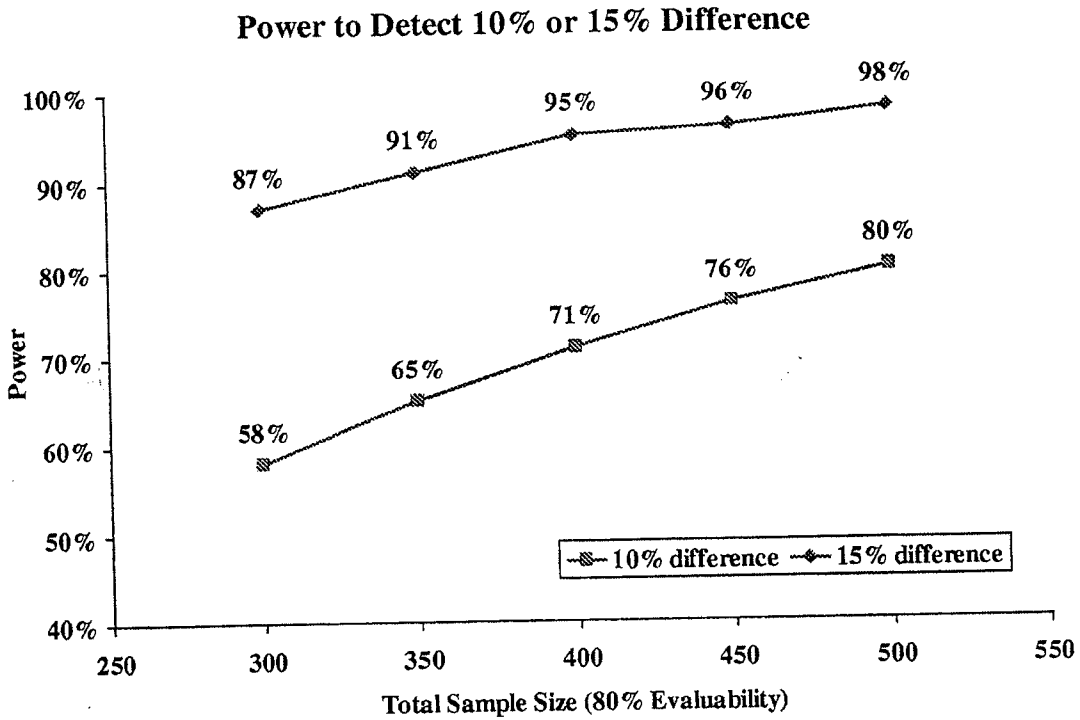
Clinical cure rates in recent sinusitis studies.

- **Original studies estimated clinical cure at >80% . –overestimation. Reduced to 75%**
- **Results in an extra 125 patients in each trial equally randomised 773 and comparator**

Drug	Cure Rate	
	PP	ITT
Ketek	75% - 91%	66% - 83%
Augmentin in KetekTx	75% - 91%	65% - 88%
Moxifloxacin	80% - 94%	NA
ABT-773	79%	73%

- The blinded ABS data in the current dose-ranging study are slightly below expectations, but fall within the range of previously accepted outcomes.

Dose-ranging studies for ABS & CAP are powered to show a 10% difference with 80% probability for 500patient sample.



- By making stopping trial at 450 patients about 2 weeks off dose decision timing

The QD/BID dose decision depends on a number of technical trade-offs.

Issue	150 mg QD	150 mg BID
Efficacy	• Blinded data suggest good efficacy. • French authorities expressed skepticism for QD dose in CAP.	• Higher probability of success in all indications, including resistance.
Safety Database	• Larger database (can use both QD and BID data).	• May need larger number of patients in a two-dose program.
Tolerability	• Higher probability of favorable profile.	• Potential for less favorable profile.
QT effects	• Lower risk of QT effect.	• Lower safety margin for QT effect given potential CYP3A interactions.
PK/PD	• Higher hurdle for dose justification.	• More favorable PK/PD assessment. • Must study diurnal variation effect.
CAP data support of ABECB	• Favorable CAP results can be used to support ABECB indication.	• Different dosing in CAP and ABECB prevents use of CAP results to support ABECB.

S. pneumoniae Isolates

- CAP- 38: 11* macrolide resistant (R) (29%): 3 ermB, 8 mefA
  - 5 penR (13%) 4 are also macrolide R, 1 is macrolide susceptible (s).
  - 773 MIC <0.25 mcg/ml for all isolates
  - 1 blood isolate clr/pen S
- Sinusitis- 28: 9 macrolide R (32%): 8 mef, 1 mef+erm
  - 4 penR (14%) 3 are macrolide R, 1 is macrolide S.
  - 773 MIC <0.12 mcg/ml for all isolates
- ABECB- 38: 9 macrolide R (24%): 4 ermB, 5 mefA
  - 2 penR (5%), both are macrolide R
  - (773 MIC <0.25 mcg/ml)
- Total- 104: 28% macrolide R;
  - 11% penR. Penicillin resistant isolates are likely (70-80%) to also be macrolide resistant. This is observed in our studies (82%).
  - No S. pneumo considered ABT-773 resistant by tentative breakpoints (0.5, 1, 2).

*8 confirmed in house

CAP update- subjects with resistant S. pneumoniae Ph 3 dosing

	Numbers (%)	MIC
Subjects enrolled	248	
Subjects with positive cultures pre rx	134 (54%)	
Subjects with S.Pneumo preRx	38 (28%, 15%)	
MRSP	11 (4%)	**3 ermB, 8 mefA 773MIC <0.25mcg/ml for all isolates**
PRSP	5 (2%)	
MRSP and PRSP	4 (80%)	

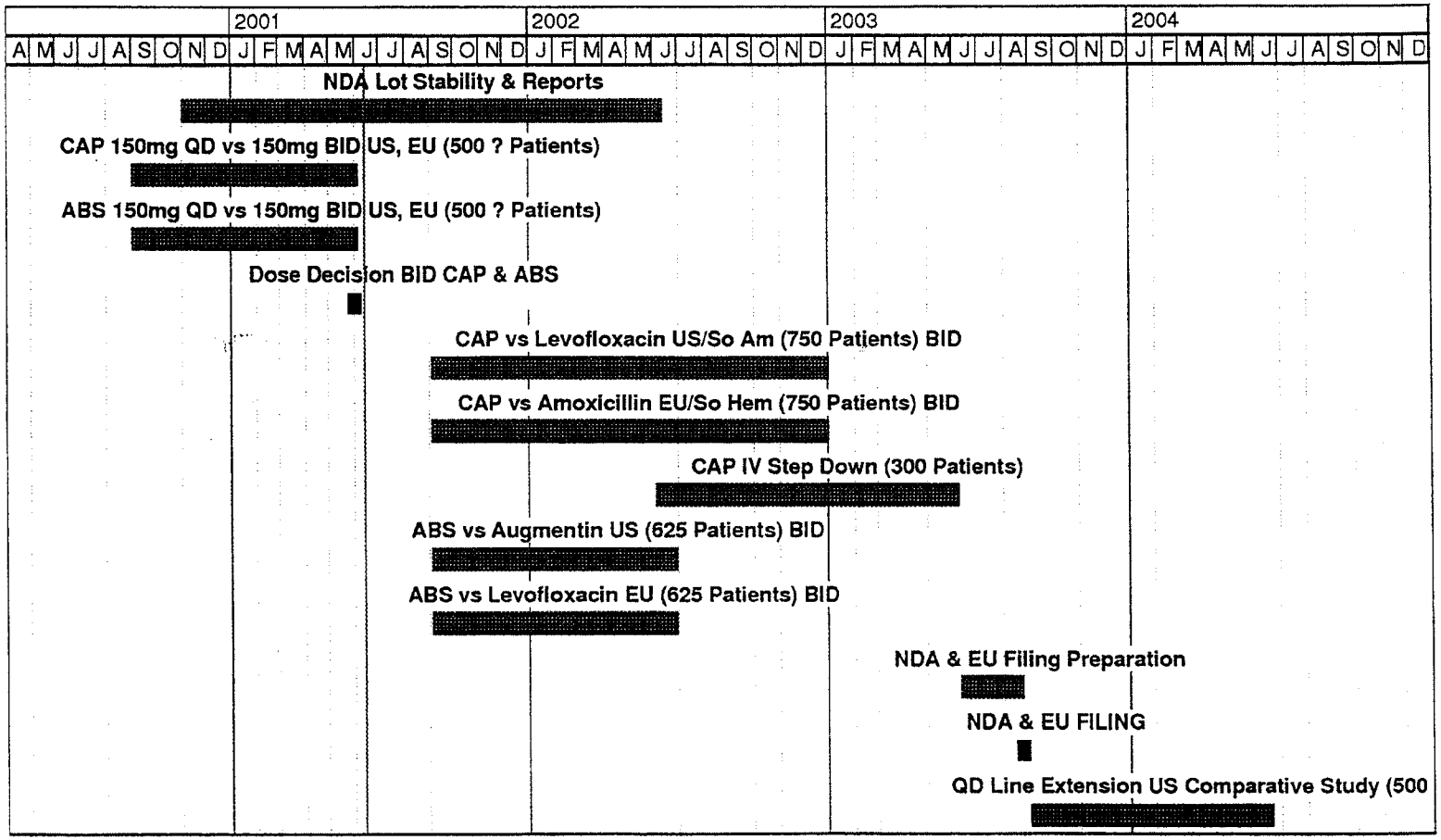
H. influenzae

CAP	- 21 H flu	773 MIC range 0.015-4.	No isolates MIC>4.
Sinusitis	40 H flu	773 MIC range 1-8.	4 isolates MIC>4.
AECB	76 H flu	773 MIC range 0.06-8.	5 isolates MIC>4.
Overall 138 H flu 9 isolates MIC=8	6.5% intermediate,.	0% resistant if using tentative breakpoints of 4, 8, 16.	

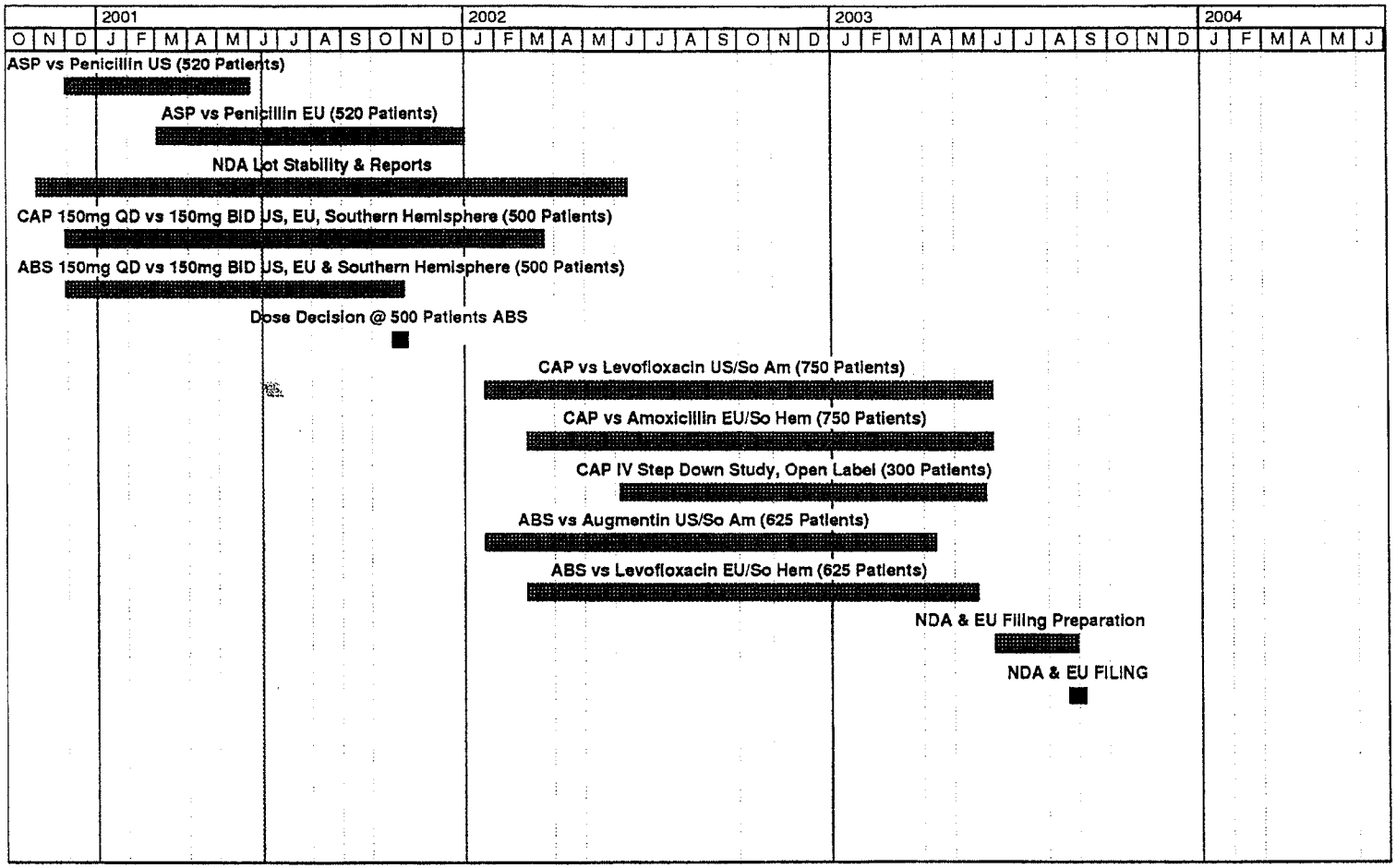
S. pyogenes

- Acute streptococcal pharyngitis trial vs.. penicillin
- 85% with positive eval 1 culture
- 21/420 isolates clari R (5%)
- 5 isolates with ABT-773 MIC >1 (1%)
  - 3 MIC=1, 2 MIC=2.
- 65/448 (15%) subjects with positive cultures at eval 4.

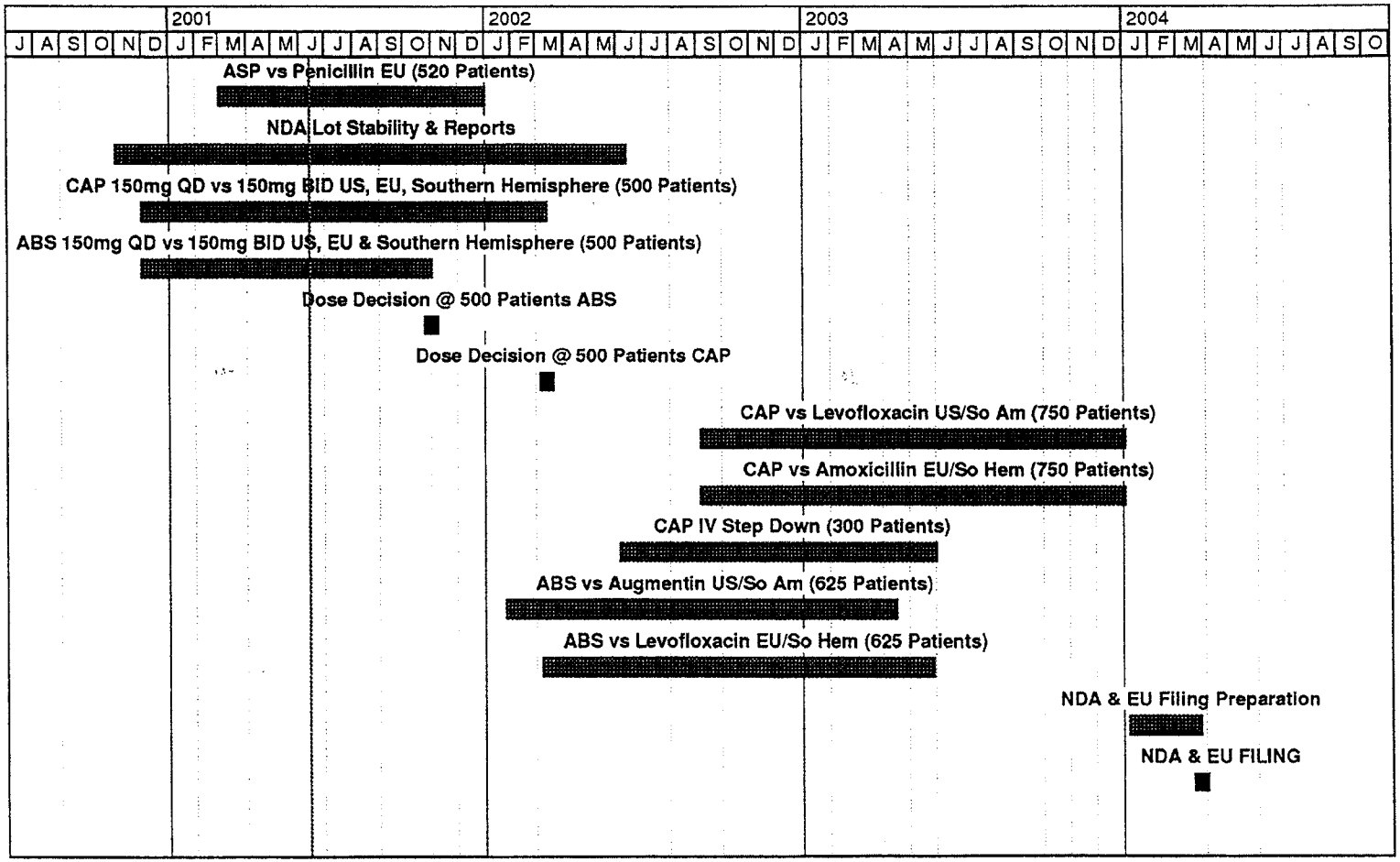
ABT-773 program timeline – Select BID today.



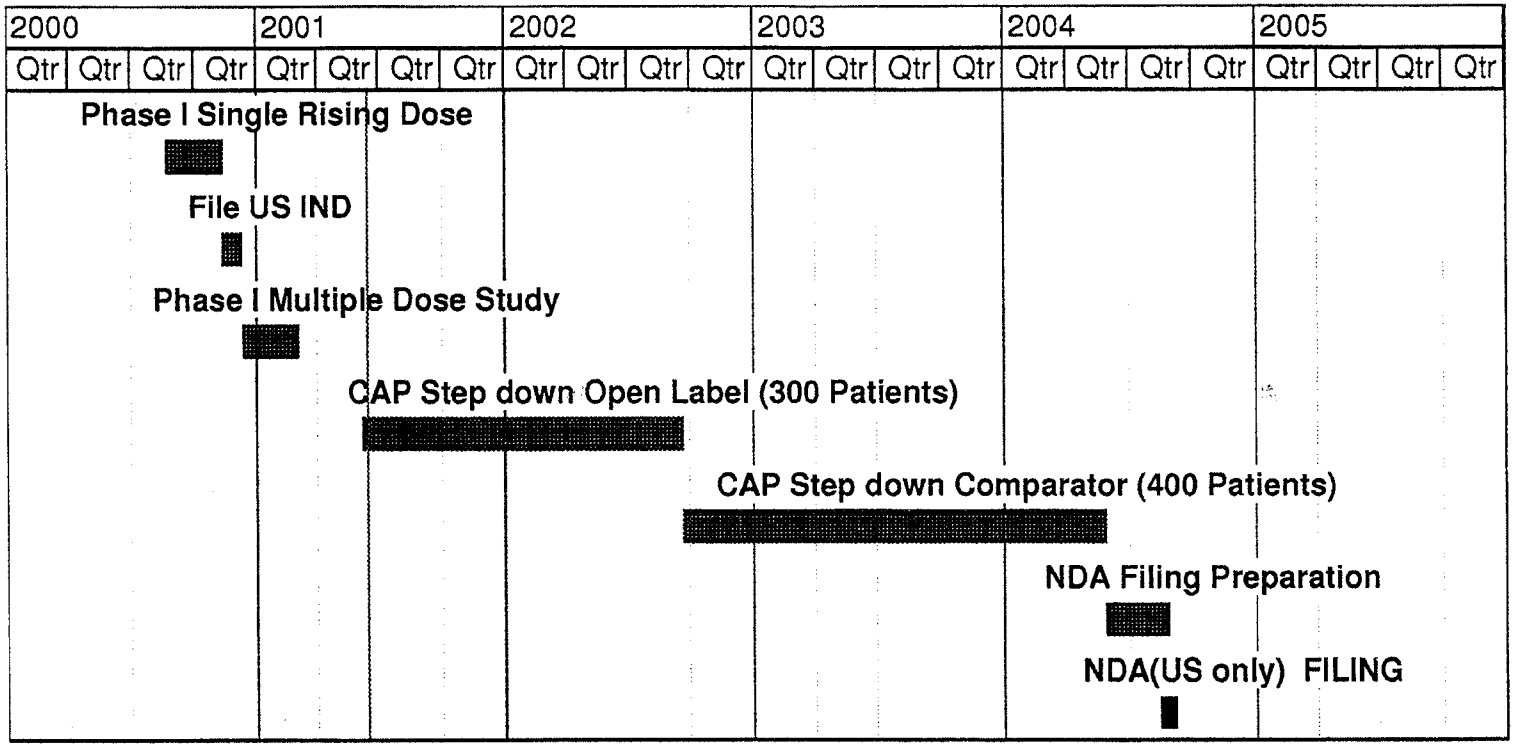
ABT-773 program timeline – Use ABS dose-ranging data only



ABT-773 program timeline – Use ABS & CAP dose-ranging data



ABT-773 program timeline – IV formulation.

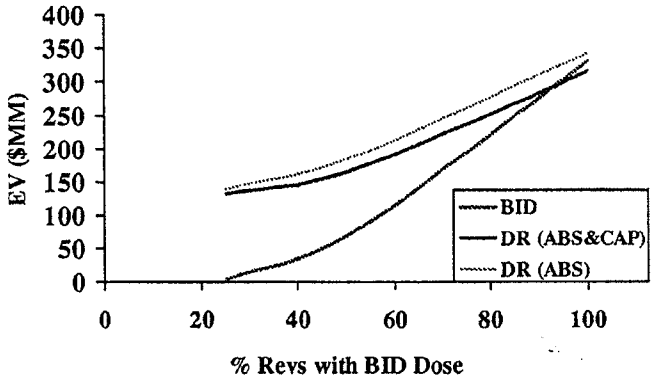


Regulatory risk is higher in the EU due to more stringent profile requirements.

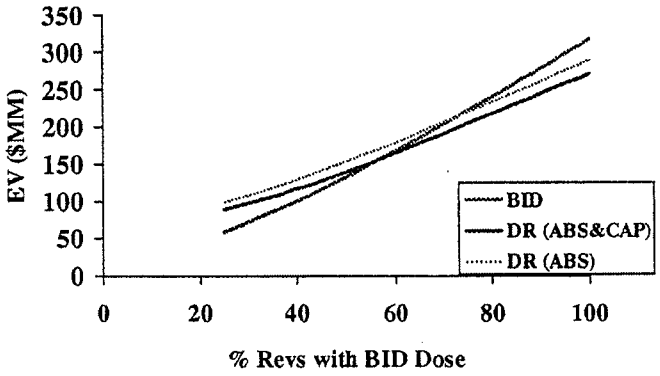
ABS	CAP	ASP	ABECB	Probability of Regulatory Success			
				No Resistance Claim		With Resistance Claim	
				US	EU	US	EU
✓	✓	✓	✓	0.90	0.90	0.95	0.95
✓	✓	✓		0.80	0.70	0.85	0.80
✓	✓		✓	0.90	0.70	0.95	0.80
✓	✓			0.75	0.50	0.85	0.60
✓		✓	✓	0.50	0.10	NA	NA
✓		✓		0.10	0.10	NA	NA
✓			✓	0.10	0.10	NA	NA
✓				0	0.10	NA	NA
	✓	✓	✓	0.75	0.20	0.85	0.30
	✓	✓		0.25	0.20	0.50	0.30
	✓		✓	0.40	0.20	0.70	0.30
	✓			0.25	0.20	0.50	0.30
		✓	✓	0	0.05	NA	NA
		✓		0	0.05	NA	NA
			✓	0	0.05	NA	NA
				0	0	NA	NA

Sensitivity to BID impact

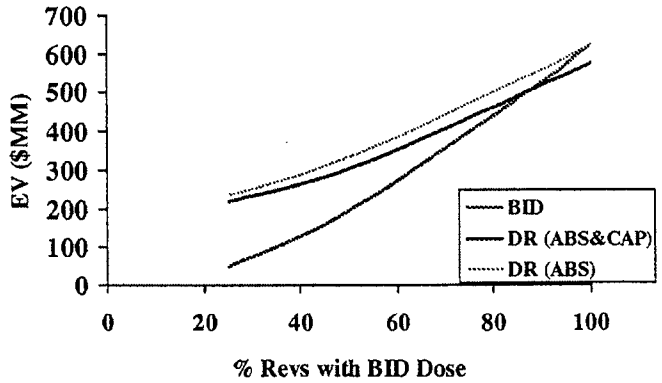
US



EU



WW



The requirements for the ABT-773 clinical development program have changed since the dose-ranging study began.

At Phase III initiation (09/00)	Since then…	Impacts on program
Planned a QD/BID dose-ranging study to find optimum dose for CAP & ABS.	Administrative delays at the FDA and slow recruitment (poor flu season) delay the study.	Unable to complete dose-ranging in time to allow for inititiation of pivotal in Sep/01 (nothern hemisphere flu season).
Safety database designed to contain 2700-3200 patients.	Ketek submitted 3700 patients, which was deemed insufficient by the advisory.	Program size increased to include ~4500 patients.
CAP pivotal designed only to achieve CAP indication – not a resistance claim.	Ketek advisory revealed the importance of the resistance claim, especially if there are safety concerns.	Regulatory approval will depend, in part, on ABT-773's ability to achieve a resistance claim.
CAP not considered a requirement for regulatory approval.	Ketek advisory heavily focused on benefit/risk, especially for CAP.	US Regulatory Affairs increases the importance of the CAP indication for drug approval.
Requirements for the resistance claim assumed to be similar to Levaquin.	Ketek submitted 17 isolates with 86% cure rate – deemed insufficient by advisory.	The size of the program has been increased to allow a 50% probability of enrolling 25 resistant isolates (double the number of CAP patients).

The dose ranging studies can lead to three possible outcomes.

Outcome		Safety Database (highest dose)		No. CAP Pts		Estimated no. isolates (50th percentile)	
ABS	CAP	Before	After*	Before	After*	Before	After*
QD	QD	4200	5300	1000	1800	17	30
BID[1]	QD[1]	1900	2050	1000	1800	17	30
BID	BID	2400	3350	750	1550	13	25

***IV studies included.**

[1] EU requires CAP & ABS at the same dose. US safety database potentially inadequate.

Extras

The BID dose has a higher probability of meeting the efficacy endpoints than QD.

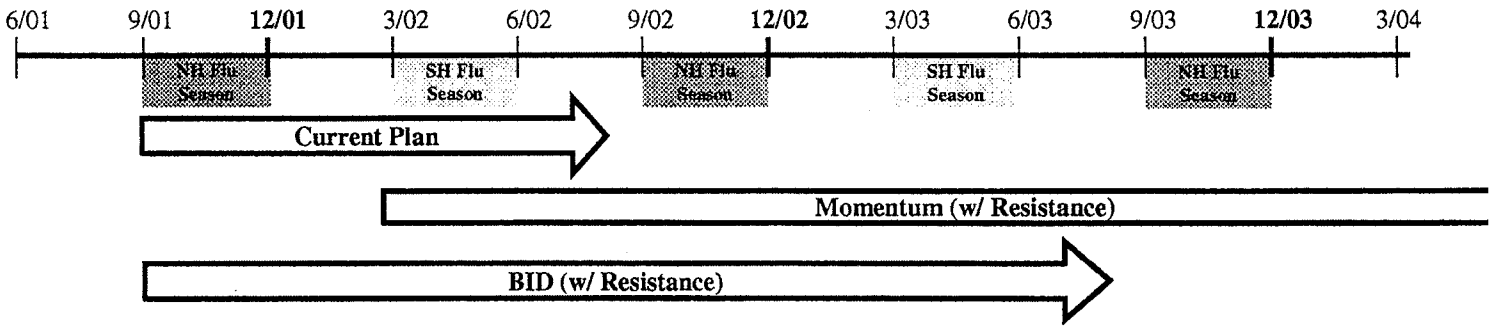
Dosing	Resistance	US	EU
QD	+	0.52	0.34
	-	0.44	0.29
BID	+	0.75	0.60
	-	0.66	0.53

- This analysis is based on today's understanding of technical risk surrounding efficacy.
  - If we learn that the QD and BID doses are equivalent in dose-ranging, then the probability of QD success increases to BID levels.
- Additional risk comes from safety issues (QT, LFT) and commercial uncertainty.

The optimum Phase III development program is a trade-off between launch timing, technical, regulatory and commercial risk.

Strategy	Dose	Filing Date	Prob Res Isolates Enrolled	Prob Safety Database Acceptable	Prob of Launch		Expected Value ($MM)		
					US	EU	US	EU	WW
Current Timeline	BID	08/02	25%	10%	0.07	0.05	-56	-38	-94
Complete Dose Ranging	QD/BID	08/04	50%	90%	0.58	0.47	157	202	359
BID @ Risk	BID	08/03	50%	90%	0.58	0.47	70*	236*	306

*** Includes optional Ph IV QD line extension.**



The ABT-773 dose selection strategy is a trade-off between technical & regulatory risk, and potential commercial payoff.

- The Ketek advisory has raised the hurdle for approval of a novel ketolide:
  - The safety database expectations have increased to 3700-4500 patients. The program incurs a one year delay to meet this goal.
  - There is an increased emphasis on the need for a CAP indication for approval of the drug.
  - The focus on benefit/risk raises the value of a resistance claim.

- To have a 50% chance of finding 25 resistant isolates, the program must evaluate 1560 CAP patients.
  - or This can be accomplished within the expanded program (4500 patients) shown above.

- The Phase III dose-ranging study is behind schedule due to FDA administrative and recruiting delays.
  - The program is delayed by up to 6 more months.
  - There is currently a 1:3 chance that these studies support the development of the 150 mg QD dose for ABS & CAP.

- The 6 month dose-ranging delay can be eliminated by selecting the 150 mg BID dose at risk for Phase III pivotal (for ABS & CAP).
  - The BID dose negatively impacts the commercial value of ABT-773, especially in the US.
  - The BID dose has a higher probability of technical success, both for ABS & CAP, and the resistance claim.

Commercial impact of indication outcomes.

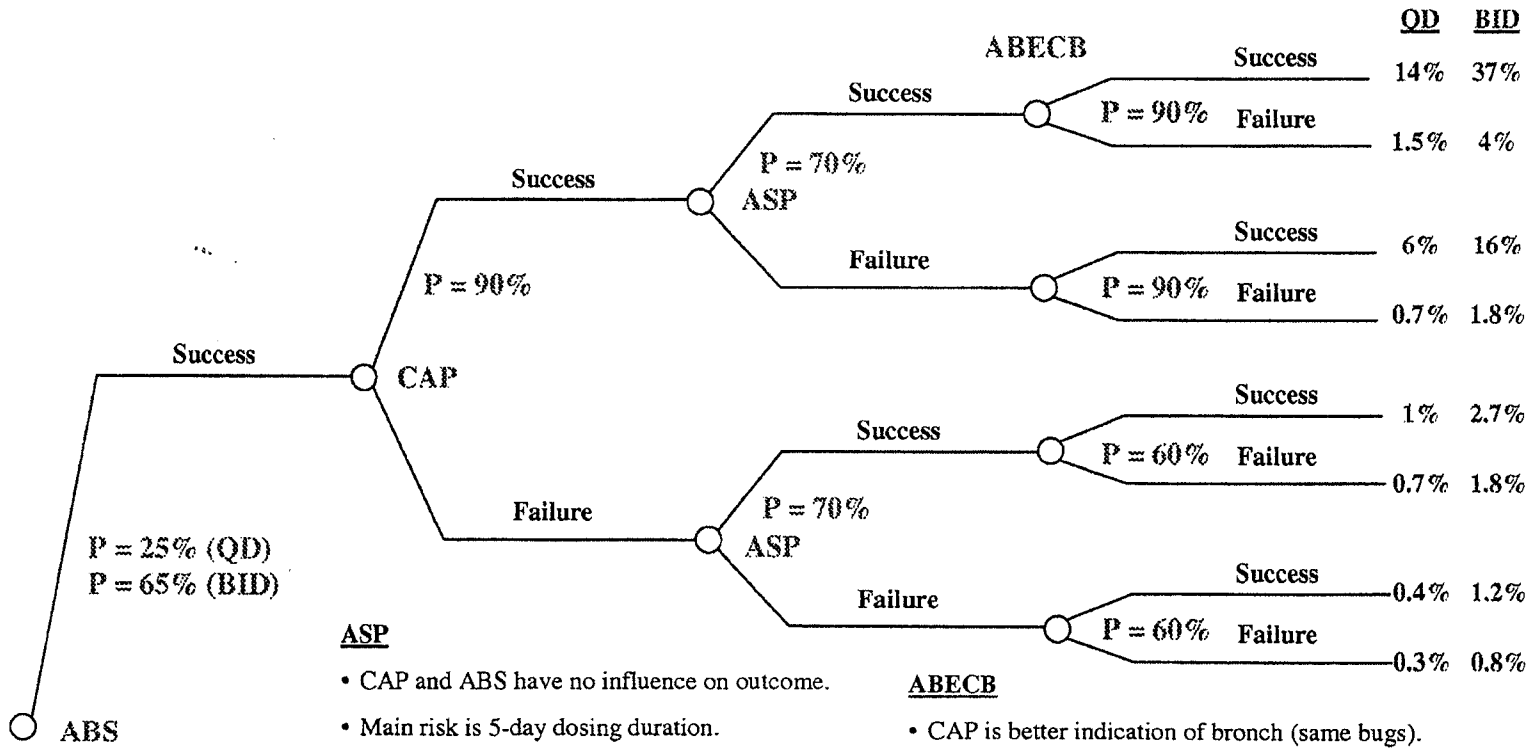
Scenario	Sinusitis	CAP	Phar	AECB	U.S. Share Impact	Revised U.S. (1)	Revised Ex-U.S.
1	Y	Y	Y	Y	0%	0%	0%
2	N	Y	Y	Y	-21%	-20%	-20%
3	Y	Y	N	Y	-12%	-5%	-33%
4	N	Y	N	Y	-32%	-25%	-53%
5	N	Y	Y	N	-63%	-90%	-53%
6	N	Y	N	N	-75%	-90%	-87%
7	Y	Y	Y	N	-42%	-70%	-33%
8	Y	Y	N	N	-54%	-70%	-66%
CAP dosed BID instead of QD (others QD)					-10%	-12%	-12%
Sinusitis dosed BID instead of QD (others QD)					-18%	-20%	-10%
Both CAP/sinusitis dosed BID instead of QD					-35%	-32%	-25%
Diarrhea rate decreases to 3% from 7%					5%	10%	5%
Diarrhea rate increases to 12% from 7%					-5%	-17%	-7%
Taste perversion descreases to 2% from 4%					5%	5%	5%
Taste disturbance increases to 6% from 4%					-5%	-7%	-5%
Penicillin resistance claim is achieved					4%	20%	25%
Macrolide resistance claim is achieved					13%	20%	25%
Both Pen-R and Mac-R claims are achieved					32%	27%	35%
Share recovery with QD Line Extension (US)					65%	5-10%	NA

1) Per Wenker/Broadhurst 6/5/01

Efficacy: Co-variance between indications (ABS success)

Asset: ABT-773
Alternative: All
Provided By: Joaquin Valdes
Date: 5/7/01

- Is the order of indications logical? From most difficult to easiest?
- Are the assessments different for QD vs.. BID?



ASP

- CAP and ABS have no influence on outcome.
- Main risk is 5-day dosing duration.
- Endpoint is eradication rather than clinical cure.
- Only need to treat *S. pyogenes*

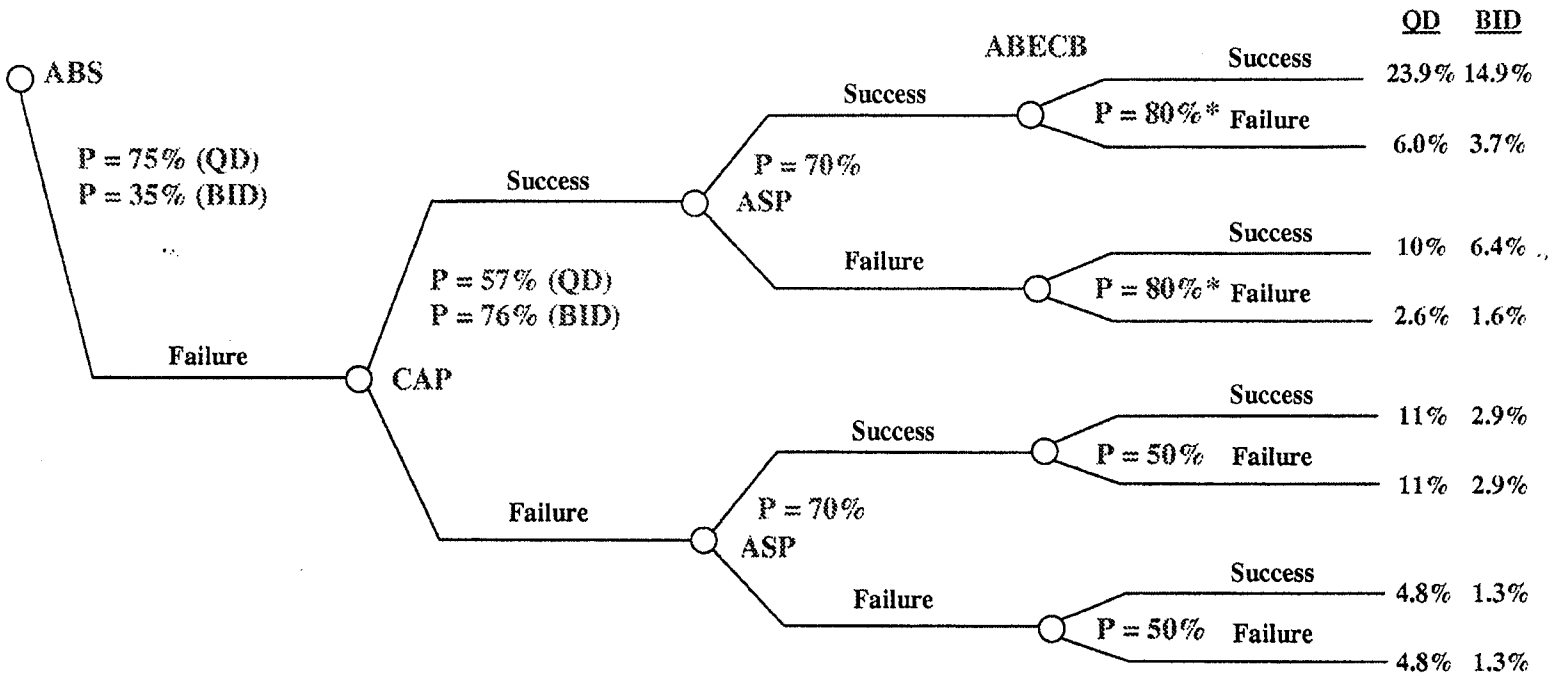
ABECB

- CAP is better indication of bronch (same bugs).
- CAP and ABECB are related.

Efficacy: Co-variance between indications (ABS failure)

Asset: ABT-773
Alternative: All
Provided By: Joaquin Valdes
Date: 5/7/01

- Is the order of indications logical? From most difficult to easiest?
- Are the assessments different for QD vs.. BID?



* Calculations based on prior assessments

ABT-773 Decision Analysis Core Team

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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

/s/ Eric J. Lorenzini
Eric J. Lorenzini (*pro hac vice*)